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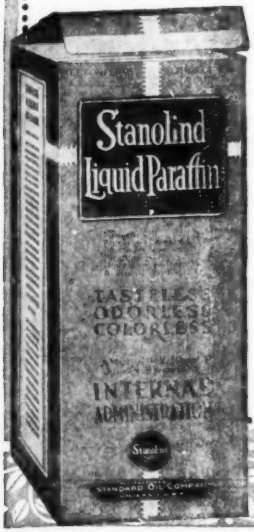

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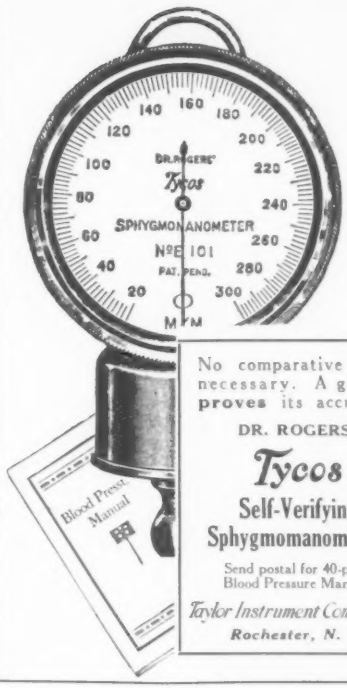

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PROFESSOR OF PHYSIOLOGICAL CHEMISTRY IN THE SHEFFIELD SCIENTIFIC SCHOOL OF YALE UNIVERSITY, NEW HAVEN, CONNECTICUT.

"Throughout the animate kingdom, from the simplest microorganisms to the most complexly organized beings, that inexhaustible power of growth which ever since the genesis of the first protoplasm in the infinite past has created the structure of the fossil remains of former ages as well as our own existence—this capacity to grow, has remained as the most remarkable phenomenon of nature, the supreme riddle of life."[2]

The problems of growth have been studied in a diversity of ways, in accordance with the special training or talents of the students who have approached them as well as in response to the contemporary tendencies in the biological sciences. The very word, growth, has come to be applied with a variety of meanings. Thus we say that a crystal grows; that bacteria grow, when they multiply in number in a medium; that a tumor or a hydrocephalus grows when its mass becomes enlarged; that a child grows. Such heterogenous phenomena can scarcely be envisaged from a single viewpoint. For the present occasion, therefore, let us direct our interest primarily to man and the higher animals, in which growth may be regarded

[1] A paper presented before the Cleveland Academy of Medicine, May 12, 1916.

[2] Rubner, M., Das Problem der Lebensdauer und seine Beziehung zum Wachstum. München, 1908, p. 81; also Ernährungsvorgänge beim Wachstum des Kindes, Arch. f. Hyg., 1908, lxvi, 81.

for the most part as reduced to a minimum when the maximum average size has been reached.

Until quite recently most of the investigations of growth, in its normal as well as its pathological manifestations, have been morphological in character. This must not be interpreted as meaning that no other mode of study has been adopted. Statistics of changes in size and other features have been accumulated. Comparative analyses of growing structures have been attempted. The dynamics of the changes in growth likewise have become the subject for speculation in the past. But the dominance of the cell and its structural changes, and the popularity of cytology, embryology, cellular pathology and the newer "Entwicklungsmechanik," have overshadowed the conception of growth which realizes that increment in size means assimilation of food and the metabolism of matter. The comparative simplicity of structure of the "lower" organisms has encouraged the pursuit of the physiology of the unicellular forms in the hope that here the problems could be more easily unravelled. There is need, however, of going beyond the beginnings of the developmental processes and of supplementing the morphological methods of study. A knowledge of cell structure alone will not suffice to define growth. The size of the organism is also of much importance. "The science of nutrition," says Bayliss,[3] "would be almost impossible without the larger, warm-blooded animals. . . . . The physiology of unicellular organisms, although of considerable importance in special aspects, is not to be regarded as 'general physiology.' Indeed, if the choice had to be made between the investigation of simple or complex organisms alone, there is no doubt that a much more general and fundamental body of doctrine would be obtained from the latter."

The factors which determine the possibility of growth, and upon which, therefore, any broad generalizations regarding the abnormalities of growth must be based may be classed, with respect to the organism involved, as internal or external in character. The *internal* factors include the real impulse to grow, of whatever nature it may be; in part they are inherited, they belong to the permanent biological characteristics of the individual. Heredity, with all that it involves, determines the most potent of these internal, constitutional incentives and conditions of growth. These are the determinants which are largely beyond our immediate control, yet must be reckoned with when defects of growth appear. The *external* factors that modify growth, on the other hand, are more amenable to directive regulation. The environment as well as the food of the individual can be modified more or less at will. Here, then, is a possible point of attack. If growth implies not only a capacity to grow, but also an actual increment of body substance, there must be

[3] Principles of General Physiology, 1915, p. 291.

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an accession of nutriment from without. The character of the food, its utilization and metabolism in health and in disease are open to investigation. The study of nutrition in growth therefore probably offers the most promising of all the modes of approaching an understanding of this fundamental biological process.

In order to have a common basis for the discussion of the abnormalities of growth some definition is essential, difficult though it may be to formulate one in entirely satisfactory terms. Even when the body as a whole no longer gains in size, individual parts like the hairs and nails may continue to grow. It will be preferable to speak of such phenomena of localized growth as a renewal of tissues, and likewise to exclude from the category of real growth the deposition of fat and other reserve materials that often produce a gain in weight. "Increment in size" or "gain in weight" or "enlargement of mass" are inadequate descriptions of the more specific characteristics of the growth of the higher forms. I have found no more helpful concise definition than that by Schloss,[4] who characterizes growth as "*the correlated increase in the mass of the body, in definite intervals of time, and in a way characteristic of the species.*"

Perfect growth and development implies a far-reaching *correlation* of the various parts of the body. An upset in this nicely balanced relationship is speedily recognized as an anomaly. Energy and matter are insufficient to explain the consummation and maintenance of a normal as contrasted with an abnormal composition of the cells. The *specificity* of growth is something marked, particularly when normal is contrasted with perverted growth. The definition referred to above has a particular value in the analysis of abnormalities of growth because it immediately suggests some of the anomalies or irregularities. Abnormal growth may involve (1) the correlation feature, or (2) a time factor whereby the characteristic rate of the increase in mass is not maintained. The correlation refers, for example, to the arrangement of matter in respect to composition (proportions of protein, water, etc.) and likewise to form. When there is overgrowth of one part or underdevelopment of another the correlation is upset. This is an abnormality. Likewise when the change in size is well proportioned or correlated, but unduly delayed or prolonged, growth becomes abnormal in its rate for the individual under consideration.

There is no ideal index or measure of growth. The most common statistics and perhaps the most satisfactory individual data are those obtained for the increments of body weight. The diagrams show the so-called curves of growth for man and for the albino rat—an animal closely related in many features of growth which has formed the subject of extensive investigations in recent years.

With these general characteristics of changes in weight during the

[4] Die Pathologie des Wachstums im Säuglingsalter, Berlin, 1911, p. 4.

period of growth in mind we may consider Fig. 3, page 5, which indicates in a highly schematic form some of the abnormalities in the rate of growth seen in the development of the young.

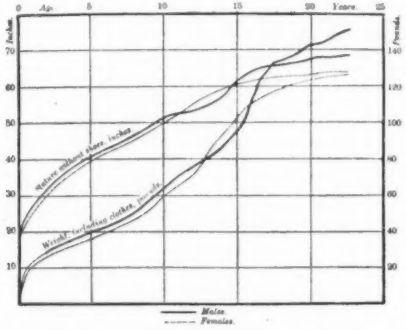

FIG. 1.—Diagram showing increase of stature and weight of both sexes, as determined by the Anthropometric Committee of the British Association. (From American Text-book of Physiology, 1896, p. 925.)

Delayed growth as the result of *external* factors can be brought about in a variety of ways associated with the food supply. Growth can be limited, of course, by an insufficient quantity of even the most appropriate food mixture. Again, there is a lower limit to

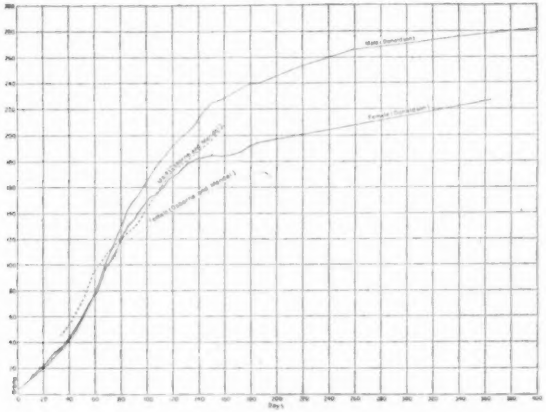

FIG. 2.—Curves of normal growth—rats. (From Osborne and Mendel and Donaldson.)

the quota of protein needed for normally rapid tissue construction, quite aside from an otherwise bountiful total energy supply. But even abundance of protein along with sufficient other nutrients may

not permit growth to continue normally, if the nitrogenous components of the diet fail to yield in suitable amounts every amino-acid required in tissue construction; for it is now an established belief among physiologists that certain of these nutrient units, such as cystine, lysine and tryptophane and doubtless others, are not constructed anew in the mammalian organism. They must be furnished as such, before new tissue containing them built up into its protoplasm can be elaborated. An appropriate supply of inorganic compounds, of lime and magnesium, of chlorid and phosphate, and perhaps of as yet unappreciated elements like iodine or manganese must sooner or later be available in the requisite minimum quantity. Finally, with all of these it now seems necessary to include a provision for the so-called food "accessories," the "vitamines" and

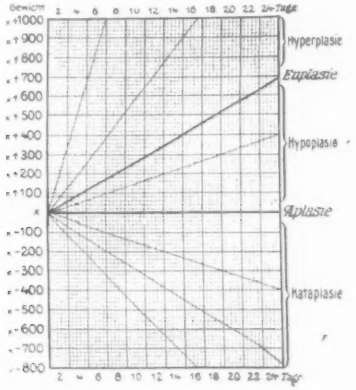

FIG. 3.—Schematic representation of abnormalities of growth. (From Schloss, Die Pathologie des Wachstums im Säuglingsalter, Berlin, 1911, p. 74.)

"auximones," which are believed to facilitate the nutrient processes and likewise, directly or indirectly, the process of growth. At any rate the failure to secure continued increment of body weight in young animals with an abundance of hitherto supposedly suitable but isolated and purified foodstuffs, and the prompt resumption of growth when very small addenda of certain natural products are furnished, leaves no other alternative than to give these accessories, seemingly insignificant though they may appear to be, due consideration in the problem of the food supply.

In discussing the nutrition of infancy Schlossmann[5] has remarked that the feeding of isodynamic quantities of food is not necessarily a guarantee of equal nutrient effects. The food must not only

[5] Beiträge zur Physiologie der Ernährung des Säuglings, Arch. f. Kinderheilkunde, liii, 1.

furnish equivalent amounts of energy, but also permit equivalent benefits to accrue to the individual that ingests it. Schlossmann therefore has suggested the term *isokerdic* (τὸ κέρδος, the gain) value to express for the equivalent biological utility of foods what the expression isodynamic indicates in respect to their comparable energy values. Repeatedly it has been observed that the addition of a seemingly insignificant amount of the non-protein, fat-free part of milk—such as the "protein-free milk" of Osborne and Mendel[6]—or of yeast (Hopkins,[7] Funk and Macallum[8]), or of plant parts containing the embryo[9] will suffice to convert failure on a given diet of isolated food substances into success. Even where one of this type of (presumably water-soluble) determinants is furnished growth may cease until some natural fat like butterfat, egg fat, or cod liver oil or

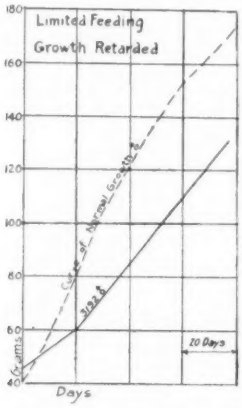

FIG. 4.—Curve of retarded growth due to limited feeding. (From Osborne and Mendel.)

fractions thereof are added to the diet. Essentials for growth that cannot be synthesized by the growing organism itself must be available in adequate amounts if the gains are to be normal in respect to the rate of growth—the time factor.

A few graphic illustrations of slow growth, exhibited in the form of curves of body weight and attributable to some of the various deficiencies of diet just discussed, are presented here. The first of these, Fig. 4, shows the effect of underfeeding with a qualitatively adequate food, in the case of albino rats.

[6] Carnegie Institution of Washington, Publication 156, Part II, 1911, p. 80.

[7] Feeding Experiments Illustrating the Importance of Accessory Factors in Normal Dietaries, Jour. Physiol., 1912, xliv, 425.

[8] Studies on Growth. II. On the Probable Nature of the Substance Promoting Growth in Young Animals, Jour. Biol. Chem., 1915, xxiii, 413–421.

[9] McCollum, E. V., and Davis, M., The Essential Factors in the Diet During Growth, Jour. Biol. Chem., 1915, xxiii, 231–246.

Fig. 5 shows the results of diets low and high respectively in the same protein.

In Fig. 6 the deficiency is exemplified by a low content of inorganic salts.

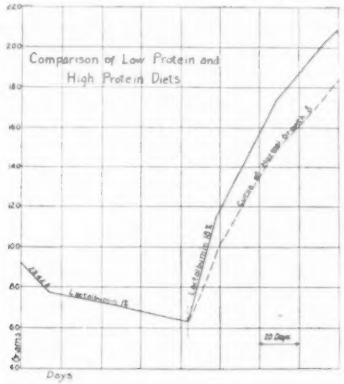

FIG. 5.—Curve showing comparative effects of diets, high and low respectively, in the same protein. (From Osborne and Mendel.)

The retarded growth, with final cessation of increase in size, seen in Fig. 7, is attributable to the lack of suitable "food accessories" in the diet.

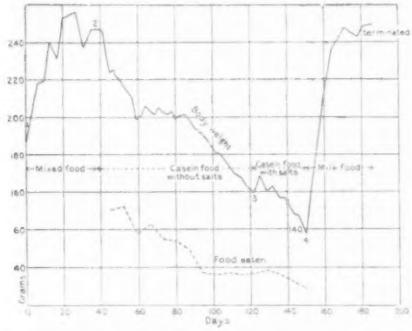

FIG. 6.—Showing effect of deficiency of inorganic salts in the diet upon growth. (From Osborne and Mendel.)

In Fig. 8 responsibility for the slow growth observed rests upon the character of the proteins fed, which failed to yield all of the amino-acids in suitable abundance.

In the preceding illustrations the growth manifested by the animals has usually been uninterrupted though proceeding at a decidedly slower rate than is normal for the species. Similar experi-

ences are familiar in the clinic for infants, but it is usually impossible to relate the retardation to a known factor as has been done in the experimental cases cited. Let there be no misunderstanding in the sense that we are attempting to refer all retardations of growth to external or dietary factors. It is merely this type of abnormality in the time relations or rate of growth that concerns us here for the moment.

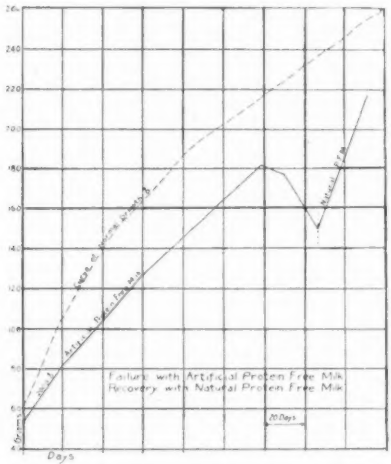

FIG. 7.—Showing effect of lack of suitable "food accessories" in the diet upon growth. (From Osborne and Mendel.)

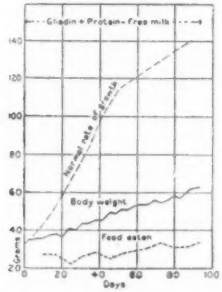

FIG. 8.—Showing failure to grow on a diet containing gliadin as the protein component. (From Osborne and Mendel.)

Complete cessation of growth in individuals not fully grown up may represent a more aggravated deprivation of some food factor essential for tissue construction—a status in which there is neither gain nor loss of weight. Such failure to grow may be observed

not only where the food supply is scanty but even where the energy content of the diet is evidently liberal. Some of the instances of "stunting" which Osborne and I have observed in our experiments with rats have been surprising in respect to the duration of the period of failure to grow. Illustrations of different types of "stunting" are shown in the following charts:

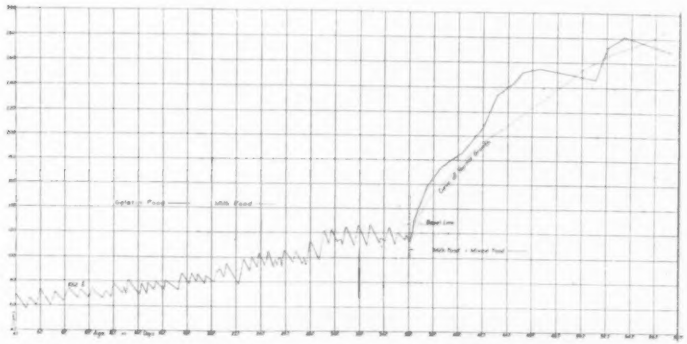

FIG. 9.—Showing prolonged failure to grow owing to inadequate character of the ration. (From Osborne and Mendel.)

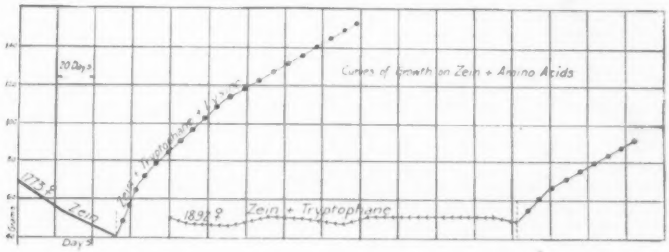

FIG. 10.—Showing failure to grow owing to a lack of the amino-acid lysine in the diet. (From Osborne and Mendel.)

Examples of this type of abnormality of growth could also readily be collected from human experience, although an equally long duration of the suppression of growth in terms of the total span of life has probably never been recorded for man. In the charts just presented it will be noted that growth was resumed in every case when an *external* factor, the diet, was altered. We are dealing here with retention of infantile characters and the capacity to grow, in many of the cases cited, at a period long beyond that at which growth is usually completed. The resumption and completion of growth after long-continued failure to grow may seem surprising in view of the wide-spread impressions that the growth impulse declines with

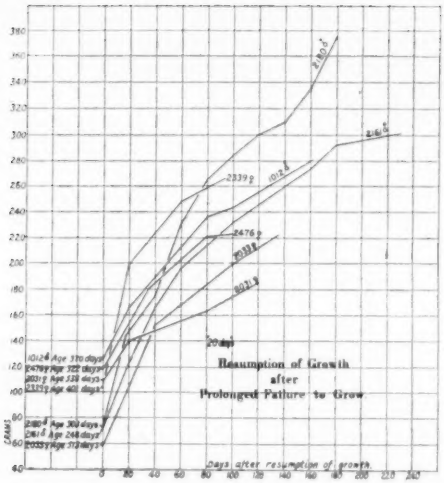

FIG. 11.—Showing resumption of growth in rats after prolonged period of suppression of growth. (From Osborne and Mendel.)

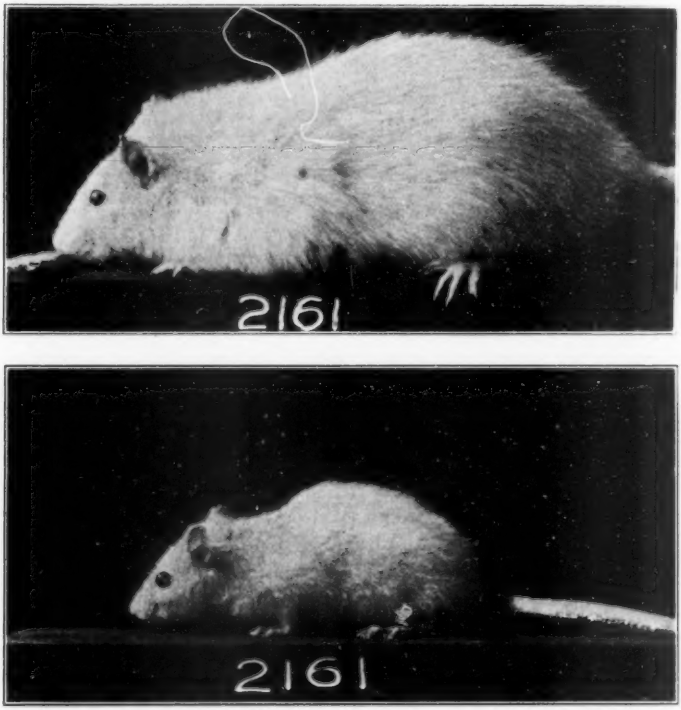

FIG. 12.—Photographs of a rat in which growth was suppressed for many months and then resumed. (From Osborne and Mendel.)

age. A few records are graphically represented in Figs. 11 and 12. The record of an infant showing a very brief delay in growth is given in Fig. 13.

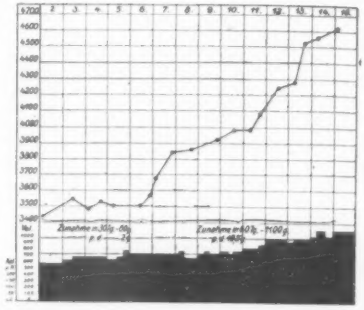

FIG. 13.—Showing the curve of suppression and resumption of growth in an infant. (From Langstein und Meyer, Säuglingsernährung und Säuglingsstoffwechsel, 1910, p. 68.)

The results of our investigation in this field have been summarized as follows:

"The growth impulse, or capacity to grow, can be retained and exercised at periods far beyond the age at which growth ordinarily ceases. In the case of our experimental animals, albino rats, in which increment of body weight ordinarily ceases before the age of 300 days, resumption and completion of growth were readily obtained at an age of more than 550 days. It is now reasonable to ask whether the capacity to grow can ever be lost unless it is exercised.

"Even after *very prolonged* periods of suppression of growth, the rats can subsequently reach the *full size* characteristic of their species. In this respect there is no impairment of the individual.

"The satisfactory resumption of growth can be attained not only after stunting by underfeeding, but also after the cessation of growth which results when the diet contains proteins unsuitable for the synthetic processes of growth or is low in protein.

"Growth in the cases referred to is resumed at a rate normal for the size of the animal at the time. It need not be slow, and frequently it actually exceeds the usual progress.

"The size or age at which the inhibition of growth is effected does not alter the capacity to resume growth. Even when the suppression of growth is attempted for very long periods at a very small size (body weight) the restoration may be adequate when a suitable diet is furnished.

"The procreative functions are not necessarily lost by prolonged failure to grow before the stage of development at which breeding ordinarily possible.

"The period of growth may be greatly prolonged by inadequacies in the diet, so that growth becomes very slow without being com-

pletely inhibited. Though the time of reaching full size is thus greatly delayed, growth, as expressed by suitable body weight, can ultimately be completed even during the course of long-continued retardation.

"The methods of partially retarding or completely suppressing growth are too varied and unlike to permit final answers as yet regarding the outcome of all of the procedures of inhibition for the subsequent welfare of the individual. Our observations apply to the effects upon size and a few other incidental features mentioned. Although it is doubtful whether the fundamental features will be altered, far reaching dogmatic statements are scarcely justifiable until the experiments have been extended to include other factors and animal species."[10]

Loss of weight, or *negative growth*, as it has been termed, is familiar not only as a manifestation of specific disease, but also as the result of malnutrition of dietary origin. Here, too, altered food supply may bring restoration of normal conditions. The "curve of repair" is unique in the rate at which changes in weight usually take place. The restoration which may follow a loss of tissues, etc., even in adult life, exceeds in its rapidity even that observed at the most vigorous periods of growth. Clinicians are well aware that recovery of weight lost during illness may take place with surprising rapidity. It seems as if the depleted body cells were ready in structure for the return of missing components without the necessity of a reconstruction of the entire fabric of the wasted tissues. A graphic expression of this is seen in Fig. 14.

Anomalies of growth expressed by an *exaggerated rate of growth* are among the rarities. Whenever the growth of an entire organism as well as that of individual organs is modified in the sense of acceleration, this usually involves repair—the reversal or return of a morbid condition to the normal as it has just been illustrated. Attention has lately been directed to the unexpectedly accelerated rate at which the increment of body weight may be resumed after growth has, for some reason or other, been inhibited for a time.[11] Fig. 15 shows that "after periods of suppression of growth, even without loss of body weight, growth may proceed at an exaggerated rate for a considerable period. This is regarded as something apart from the rapid gains of weight in the repair or recuperation of tissue actually lost. Despite failure to grow for some time the average normal size may thus be regained before the usual period of growth is ended."

Analogous conditions in infants seem to be represented by the

[10] Osborne and Mendel, The Resumption of Growth after Long-continued Failure to Grow, Jour. Biol. Chem., 1915, xxiii, 439–454.

[11] Osborne and Mendel, Acceleration of Growth after Retardation, Am. Jour. Physiol., 1916, xl, 16–20.

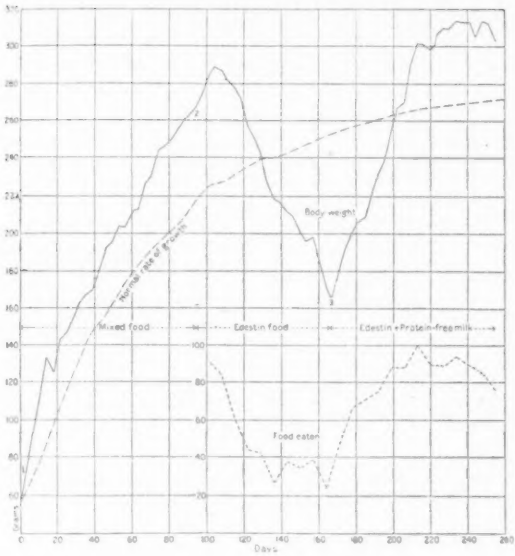

FIG. 14.—Curves showing restoration after depletion of body weight in rats. (From Osborne and Mendel.)

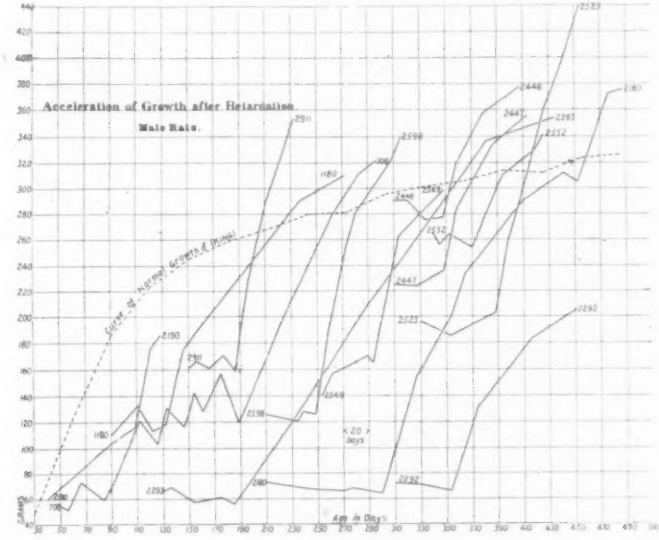

FIG. 15.—Showing curves of acceleration of growth after retardation of growth. (From Osborne and Mendel.)

following case of failure to gain weight in scurvy and the resumption of growth under the influence of orange juice added to the diet.[12]

The foregoing experiences respecting the ability of the individual to make exceptionally rapid gains of weight after periods of enforced maintenance without growth have led us to raise certain questions of broader biological interest. "What has time accomplished in the interval of unchanged total body weight? Have developmental changes or cellular rearrangements proceeded? Have some of the cells (perhaps those of certain endocrine glands) advanced in their development more nearly normally than the great mass of the tissues? If so, they might exert an undue stimulus upon the energy transformations leading to growth."[13] The inquiries here submitted may properly introduce a second phase of our subject, the *abnormalities*

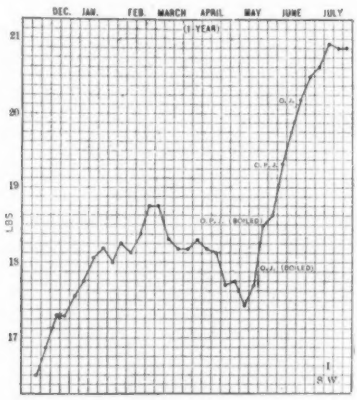

FIG. 16.—Showing curve of accelerated growth in an infant after failure to grow. (From Hess, 1916.)

of correlation in growth. The interrelations of proportion in the parts of the body may vary not only among individuals and species, but also in the same individual at different stages of development, as is shown in Fig. 17.

Precisely as there are changes in the correlation of form or morphological structure, so there may be alterations in the distribution of chemical components of the body, the upset of which represents abnormality. Thus Aron has indicated that the form of animals maintained at stationary weight before they are fully grown may change. They may grow in stature, one part changing at the

[12] Hess, A. F., The Influence of Infantile Scurvy on Growth (Length and Weight), Proc. Soc. Exper. Biol. and Med., 1915, xiii, 50.

[13] Osborne and Mendel, Acceleration of Growth after Retardation, Am. Jour. Physiol., 1916, xl, 16.

expense of another.[14] This is seen in Fig. 18, in which the same rat was photographed at intervals of forty-seven days, during which there was no increment in total weight.

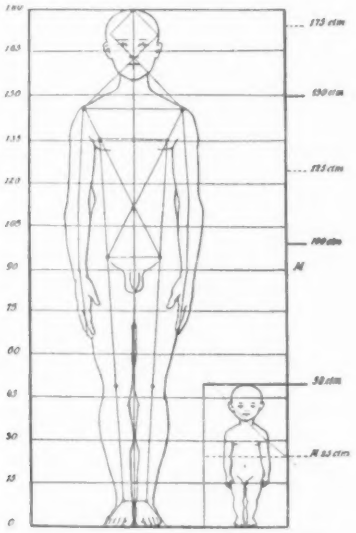

FIG. 17.—Showing changed proportions of the body of man accompanying growth. (From Stratz, Der Körper des Kindes, 1904, p. 57.)

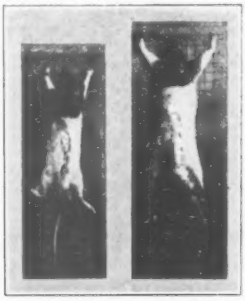

FIG. 18.—Showing changes of form with stationary body weight. (From Aron, 1912.)

The change of form noted by Waters[15] in young cattle underfed so as to keep their weight stationary is also evidence of correlative

[14] Aron, H., Weitere Untersuchungen über die Beeinflussung des Wachstums durch die Ernährung. Verhandlungen der 29sten Versammlung der Gesellschaft für Kinderheilkunde in der Abteilung für Kinderheilkunde der 84. Versammlung der Gesellschaft deutscher Naturforscher und Aerzte in Münster, 1912, 99–103.

[15] The Influence of Nutrition upon the Animal Form, Proceedings of the Society for the Promotion of Agricultural Science, 1909, xxx, 70; also XVII. Biennial Report, Kansas State Board of Agriculture, 1911, xxii, 199.

changes. Apparently the skeleton has grown in these cases at the expense of other parts. It is doubtless true, as Aron has indicated, and as has been shown in unpublished experiments by Dr. Judson in the writer's laboratory, that the inorganic components of the skeletal parts may continue to increase while the body, as a whole, is failing to gain in weight.

Defective bone growth is undoubtedly concerned in a variety of abnormalities of development. A quotation from McCrudden[16] may serve to illustrate some of the problems involved:

"Another kind of condition in which bone growth is involved is dwarfism. The causes are probably many. But in one type I have observed a disturbance of calcium metabolism associated with improper development of bone. Calcium is almost absent from the urine, leading to the belief that the blood must be poor in calcium or contain it in some unusual combination. The feces are very rich in calcium, containing sometimes more than the food. There is, in fact, a flux of calcium through the feces. And in these cases the long bones fracture easily and roentgen-ray examination shows a very thin cortex. In other types there are no abnormalities of this kind. Now, as pointed out by Rubner, we can imagine two fundamental causes for the lack of growth: (1) the lack of what might be called the tendency to grow, that property which is present in young animals, but absent in adults, and (2) the absence of the material for growth. And it seems to me that in these two types we have examples of disturbances of each of these two factors. In the one the skeleton is growing as fast as the material at its command permits. We might almost say that it is growing too fast, for it is growing in length at the expense of solidity. In the other there is no such tendency to grow. There is calcium enough present to form longer bones, but there is no tendency to form them. And this kind of disturbance of bone nutrition we may refer to as a quantitative change, for the bones fail to grow in size. There are two large subdivisions of this type—one in which the tendency to grow is absent, the other in which the material for growth is not available."

There is occasion to believe that the growth of bone in the young is only one of the developmental processes under the physiological dominance, so to speak, of the endocrine or ductless glands. The thyroid, thymus, ovary, testis, hypophysis and others, furnishing inhibitory as well as facilitating factors, may be involved. The effects of removal or loss of function of some of these glands upon growth are being investigated in a more systematic manner. The results of gonadectomy are perhaps most familiar. Many of the peculiar phenomena in respect to the evolution of stature, the secondary sex characters, psychical aberrations and their deviations from the usual mode of development induced by experiments in

[16] The Nutrition and Growth of Bone, Transactions of XV International Congress on Hygiene and Demography, Washington, September 23–28, 1912.

growth find an analogue in human cases of infantilism.[17] Sexual infantilism must be differentiated from another abnormality of childhood to which Herter[18] gave the name *intestinal infantilism*. This is a pathological state marked by a striking retardation in growth of the skeleton, the muscles and the various organs and associated with a chronic intestinal infection characterized by the overgrowth and persistence of bacterial flora belonging normally to the nursling period. The chief manifestations of intestinal infantilism are: Arrest in the development of the body; maintenance of good mental powers and a fair development of the brain; marked abdominal distention; a slight or moderate or considerable degree of simple anemia; the rapid onset of physical and mental fatigue; irregularities of intestinal digestion resulting in frequent diarrheal seizures. A type of infantilism associated with poor nutrition due to the defective circulation dependent on a congenital or acquired cardiac defect (vitium cordis) is shown in Fig. 19.

FIG. 19.—Showing infantilism in a youth, aged sixteen years, in contrast with a normal individual of the same age. (From Peritz, 1911, p. 460.)

It will be noted that the interferences with normal growth may be constitutional, or internal, in some of these manifestations of abnormalities of correlation, and external or seemingly associated with alimentation in other cases. It is not yet possible to distinguish clearly between cause and effect. Normal development of the endocrine glands (upon which in turn properly correlated growth depends) may often be conditioned upon a suitable food supply. It is thus quite conceivable, as several writers have pointed out, that the inevitable need of specific amino-acids or "food accessories" is

[17] Peritz, G., Der Infantilismus. Ergebnisse der inneren Medizin und Kinderheilkunde, 1911, xvii, 405.

[18] On Infantilism from Chronic Intestinal Infection, New York, 1908.

occasioned not alone by its value as a direct constructive unit in the growing body, but equally well because it plays some role in facilitating the function of some ductless gland. The supposed relation of iodine to the thyroid gland at once presents itself as a possible illustration. Complex pluriglandular regulatory inter-relations have often been discussed of late.

Only hasty and fragmentary reference can be made here to the more recent interesting observations of Cushing,[19] Goetsch,[20] and others on the possible relations of the pituitary gland and its disorders to growth; to the investigations of McCord[21] and of Dandy[22] on the pineal body; to the studies of Pearl,[23] Robertson,[24] and others on the feeding of pituitary and corpus luteum to growing animals.

It is too early to draw any sweeping conclusions from the already extensive literature on the ductless glands; but one may look forward with confidence to interesting developments in this field of the physiology and pathology of growth. Future investigation may show that directive influences in growth reside in the endocrine glands to an extent scarcely realized at present; possibly it will be found that the correlative factor which has been emphasized in this review is closely bound up even more closely than can now be appreciated with the proper growth and development of such special tissues.

A remarkable illustration of the potent effect of substances derived from the ductless glands has been furnished by Gudernatsch[25] and verified and extended by other investigators (Romeis[26]

[19] The Pituitary Body and its Disorders, Philadelphia, 1912.

[20] The Influence of Pituitary Feeding upon Growth and Sexual Development, Bull. Johns Hopkins Hosp., 1916, xxvii, 29.

[21] The Pineal Gland in Relation to Somatic, Sexual and Mental Development, Jour. Am. Med. Assn., 1914, lxiii, 232–235. The Pineal Gland in Relation to Somatic, Sexual and Mental Development, second paper, Jour. Am. Med. Assn., 1915, lxv, 517–520.

[22] Jour. Exper. Med., 1915, xxii, 237.

[23] Studies on the Physiology of Reproduction in the Domestic Fowl. XIV. The Effect of Feeding Pituitary Substance and Corpus Luteum Substance on Egg Production and Growth, Jour. Biol. Chem., 1916, xxiv, 123–135.

[24] Experimental Studies on Growth. III. The Influence of the Anterior Lobe of the Pituitary Body upon the Growth of the White Mouse, Jour. Biol. Chem., 1916, xxiv, 385–396. Experimental Studies on Growth. IV. The Influence of Tethelin, the Growth-controlling Principle of the Anterior Lobe of the Pituitary Body upon the Growth of the White Mouse, Jour. Biol. Chem., 1916, xxiv, 397–408.

[25] Feeding Experiments on Tadpoles. I. The Influence of Specific Organs Given as Food on Growth and Differentiation, Archiv f. Entwickelungsmechanik der Organismen, 1912, xxxv, 457–483. Feeding Experiments on Tadpoles. II. A Further Contribution to the Knowledge of Organs with Internal Secretion, Am. Jour. Anat., 1914, xv, 431–474. Feeding Experiments on Rats. III. A Further Contribution to the Knowledge of the Organs with an Internal Secretion, Am. Jour. Physiol., 1915, xxxvi, 370–379.

[26] Der Einfluss verschiedenartiger Ernährung auf die Regeneration bei Kaulquappen (Rana esculenta). I. Archiv f. Entwicklungsmechanik der Organismen, 1913, xxxviii, 183. Experimentelle Untersuchungen über die Wirkung innersekretorischer Organe. II. Einfluss von Thyroidea- und Thymusfütterung auf das Wachstum, die Entwicklung und die Regeneration von Anurenlarven, Archiv f. Entwicklungsmechanik der Organismen, 1914, xl, 571.

and Cotronei[27]). A number of mammalian organs, especially those with an internal secretion: thyroid, thymus, adrenal, testis, ovary, hypophysis, liver, muscle, etc., were given as food to tadpoles of *Rana temporaria* and *esculenta*. It was seen that each organ exerted a certain influence on growth and differentiation of the animals. Most striking was the influence of the thyroid food. It caused a precocious differentiation of the body, but suppressed further growth. The tadpoles began to metamorphose a few days after the first application of the thyroid, and weeks before the control animals did so. The influence of the thymus was quite the opposite. Especially during the first days of its application it caused a rapid growth of the animals, but postponed the final metamorphosis or suppressed it completely. The appearance of tadpoles fed on thymus and thyroid respectively is shown in Fig. 20.

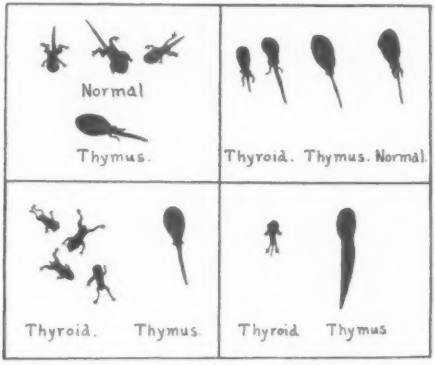

FIG. 20.—Showing effects of feeding thyroid and thymus to tadpoles.

Abderhalden,[28] from whose paper part of these illustrations are taken, has found that the thymus, thyroid, and other glands may be subjected to digestion by pepsin, trypsin, and erepsin successively, until the protein test is no longer obtainable; yet the products of digestion still contain the substances which either promote or suppress differentiation and modify growth. Combinations of several glands fed simultaneously may produce grotesque animal forms. A new field of investigation has been opened.

In the future it will be necessary to reckon with the probability

[27] Première contribution expérimentale à l'étude des rapports des organes dans la croissance et dans la métamorphose des Amphibies anoures. L'influence de la nutrition avec la thyréoide des mammifères, Archives italiennes de biologie, 1915, lxi, 305.

[28] Studien über die von einzelnen Organen hervorgebrachten Substanzen mit spezifischer Wirkung. I. Verbindungen, die einen Einfluss auf die Entwicklung und den Zustand bestimmter Gewebe ausüben, Pflüger's Arch., 1915, clxii, 99.

that growth in the sense in which we have defined it is dependent upon many factors, some of which facilitate, while others may retard the orderly progress of the process. A given environment may be disadvantageous, not only because it presents harmful or inhibitory influences, but also because it fails to manifest those that promote growth. The effect which nutrition may exert is only part of the story of growth; but it is a factor regarding which helpful information is being accumulated and one which is subject to immediate modification in a way that hereditary factors are not. Much commendable effort is being expended in improving the environment of the human individual during the period of growth. The current interest in the food hygiene of infancy, the school lunch problem, and related topics bear witness to this. These endeavors in the field of enlightened philanthropy, and public welfare should rest, as far as present-day knowledge will permit, on the basis of scientific information.

Traditions regarding growth and its perversions must give way to tested truths. It matters little if some of the determinants have not yet been discovered—if the limited experience of the laboratory fails to cover all the problems of the home and the clinic. Some real progress has been revealed, so that there is a sense of satisfaction even in relation to the obscure questions which have here been reviewed, in hearing Karl Pearson's[29] conclusion respecting the claims of science. He says: "For the present, then, it is better to be content with the fraction of a right solution than to beguile ourselves with the whole of a wrong solution. The former is at least a step toward the truth, and shows us the direction in which other steps may be taken. The latter cannot be in entire accordance with our past or future experience, and will therefore ultimately fail to satisfy the æsthetic judgment. Step by step that judgment, restless under the growth of positive knowledge, has discarded creed after creed, and philosophic system after philosophic system. Surely we might now be content to learn from the pages of history that only little by little, slowly line upon line, man, by the aid of organized observation and careful reasoning, can hope to reach knowledge of the truth, that science, in the broadest sense of the word, is the sole gateway to a knowledge which can harmonize with our past as well as with our possible future experience. As Clifford puts it, 'Scientific thought is not an accompaniment or condition of human progress, but human progress itself.'"

[29] The Grammar of Science, London, 1900.

SYPHILIS OF THE STOMACH: A CLINICAL AND ROENTGENOLOGICAL STUDY, WITH A REPORT OF TWENTY-THREE CASES.*

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The rarity of syphilis of the stomach is generally conceded, and it is largely on account of its rarity that the disease is of unusual interest. However, from my own observation and that of contemporaries it is safe to say that the condition has a greater incidence than is commonly supposed. Because of a more or less well-grounded skepticism, and because of the possibility of unfavorable criticism, the clinician is constrained to limit his reports to those cases in which the proof of the existence of the disease is most convincing. Objections to clinical diagnosis may be carried so far as to be unscientific. Evidence produced to support the specificity of the lesion in the absence of postmortem examination or microscopic study of resected tissue may be as logical and decisive as many other facts of medicine that are freely accepted.

The earlier literature of gastric syphilis has been thoroughly reviewed by recent contributors to the subject, the survey embracing the histopathological and gross anatomical descriptions and clinical classifications which constitute the basis of our present knowledge. For convenience, this literature may be divided into three periods, the first extending from the classical report of Chiari[1] in 1891 to the year 1905, the second, from 1905 to 1910, and the third, from 1910 to date. The literature of the first period deals largely with postmortem material. In that of the second period, though a number of cases are reported, the diagnosis rested largely on the history and antispecific treatment. During the third period serology and roentgenology proved useful agents in supplying the data necessary for diagnosis. In 1912, in a comprehensive review, Meyers[2] tabulated 58 cases, among which were included those reported by Birch-Hirschfeld, Fränkel, Dieulafoy, Fournier, Hemmeter, Flexner, Einhorn, Hayem, Rudnitzki and others. More recent articles dealing with the subject, and giving case reports, are those of Holitsch,[3] Mills,[4] McNeil,[5] Myer,[6] Morgan,[7] Tuohy,[8] Cronin,[9] Brunner,[10] Lensman,[11] Downes and Le Wald,[12] Brugsch and Schneider,[13] Hausmann,[14] Meuhlmann,[15] Smithies,[16] and Niles.[17] To date, our own observations have included 23 cases, a number which seems sufficiently large to warrant certain conclusions.

Symptoms and Diagnosis of Gastric Syphilis. Syphilis of the stomach, as a rule, is a late manifestation of the disease both

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in the congenital and the acquired form, although in the former it may be present early in life. Briefly stated, the gross lesions are concerned chiefly with (1) the gumma in its various forms, and (2) diffuse syphilitic infiltration. It is generally conceded that the clinical picture as such may be much like that of non-specific gastric disease, but that usually the results obtained from therapy in the two conditions are different. Many clinicians suspect lues as the etiological factor in cases of atypical gastric disturbances that do not respond to ordinary dietetic and medical management, a suspicion very frequently justified. Heretofore no characteristic syndrome has been noted or suggested, largely because of lack of sufficient material and doubt as to whether the diagnosis of gastric syphilis was correct. In one instance, a circumscribed lesion, such as a gummatous infiltration of the pylorus, with cicatrization and resulting stenosis, may so closely simulate benign simple ulcer or even carcinomatous ulcer in all its clinical aspects as to defy differentiation. In another, owing to the presence of multiple lesions with their sequelæ or extensive involvement in one and the same organ, the symptoms presented may be so variable as to preclude proper clinical recognition or classification.

The diagnosis of syphilis of the internal organs is based usually on the past history with regard to the initial and secondary symptoms, on the demonstration of late syphilitic manifestations, Wassermann-Noguchi reactions, and the results of specific therapy. In gastro-intestinal cases the Wassermann test is the most helpful means of differentiating syphilitic ulcers, circumscribed or diffuse gummatous deposits, proliferative infiltrations and their sequelæ (cicatrices, ulceration and fibrous hyperplasia) from simple ulcers and other diseases of the stomach, particularly carcinoma. Often, however, the diagnosis of gastric syphilis is made accidentally. The absence of a history of syphilis, abortion, sterility, or a negative Wassermann reaction does not exclude the possibility of syphilis. Our own series of cases have taught us this fact plainly. On the other hand, while objective signs of active, latent, or obsolete syphilitic lesions elsewhere (in the bones, glands, skin, nasopharynx, aorta, special sense organs, stigmata) may suggest that the cause underlying the gastric disturbance is specific, such signs are usually absent or not apparent, except in cases of congenital syphilis. Of the greatest importance as indicating gastric syphilis is the combination of anacidity, subacidity, or achylia, with a syndrome approximating, but not exactly resembling, that of benign ulcer in some respects, and that of gastric carcinoma in others, and accompanied by roentgenological findings suggestive mainly of carcinoma. These factors in addition to a positive Wassermann reaction or a history of infection and other features to be mentioned later are strong presumptive evidence of gastric lues. However, the fallacy of concluding that a gastric lesion is necessarily luetic if

accompanied by a consistently positive Wassermann reaction must be avoided. The coexistence of syphilis with benign and malignant gastric disease having no obvious etiological relationship is not uncommon. On that account we have been obliged to discriminate closely in the presence of a positive Wassermann, excluding, as non-syphilitic, cases with a fairly regular syndrome, normal or increased acid values, in which the gross macroscopic appearance at the time of operation or the microscopic picture of the resected tissue was that of the usual chronic calloused gastric ulcer, and in which the improvement in gastric function was complete or satisfactory without antispecific treatment.

The criticism may be advanced that in making this distinction we have disregarded or overlooked the early uncomplicated syphilitic ulcer or circumscribed gumma, the former of which has been and is still regarded by many as the commonest form of gastric syphilis, and that, therefore, the material herewith presented represents only cases in which the disease was advanced. Such criticism is not justified by the facts to be presented herewith. The most accurate differentiation of early syphilitic gastric ulcer from non-syphilitic lesions of the stomach can be made only from the study of the symptomatology, gastric chemistry, serodiagnosis, gross pathology, roentgenology, and the results of specific therapy in both. Unfortunately our knowledge bearing on various problems of the subject is still incomplete because the cases reported have not been studied in all these phases. It may be said, however, that the role played by syphilis in the etiology of gastric ulcer is doubtful because of the following facts: (1) the rarity of cases in which the two are associated —only $\frac{1}{3}$ of 1 per cent. in our series of over 2500 operatively demonstrated cases of benign gastric and duodenal ulcer; (2) the results of Rosenow's[18] research in regard to the streptococcal origin of gastric and duodenal ulcers; (3) lack of evidence to show that simple ulcer becomes gummatous in the presence of systemic or gastric syphilis, as stated by Brugsch and Schneider.

In view of our slowly increasing knowledge with respect to the pathology of visceral syphilis in general, and gastric syphilis in particular, there is some reasonable doubt as to the frequency of uncomplicated syphilitic ulcer; moreover, when this type of lesion presents itself, other factors are invariably associated which in our experience has not made the specific nature of the lesion difficult to establish in most instances. In accordance with the original view of Klebs, Fränkel and others we recognize as actually specific only those ulcers resulting from the degeneration of a gumma. Such have been reported in considerable number in the literature, yet only one was found in Chiari's postmortem material of 98 cases. There is, however, a considerable difference in the gross pathology of benign and gummatous ulcers that is quite apparent

to the experienced surgeon or pathologist on ordinary examination. The latter are invariably multiple, have a predilection for the cardia, the lesser curvature, and especially the pyloric portion of the stomach. Usually they are associated with perigastric adhesions, proliferative hyperplasia of the gastric walls and other sequelæ resulting in gastric deformity. To the clinician and roentgenologist these characteristics in conjunction with a markedly altered chemistry rather suggest carcinoma than benign ulcus callosum.

Review of Cases. The 23 cases that have come under my observation have been either operatively demonstrated or clinically observed, and therapeutically managed in the general surgical and medical divisions of the Mayo clinic during the last seven years. With one exception all were of the acquired type of gastric syphilis.

Clinical Consideration. Sex. In the 23 cases there were 17 males (74 per cent.) and 6 females (26 per cent.) or about 3 males to each female. This is almost the sex ratio of benign chronic gastric ulcer.

Age. The youngest patient in the series was twenty, the oldest fifty-seven years. More than two-thirds were below the age of forty. The average age of both males and females was thirty-five. It will be recalled that the average age of the patients having non-malignant ulcers was forty-three years and that of cancerous patients about fifty-four.

Etiology. The number of patients admitting luetic disease was 13, or a little more than one-half. Twelve (52 per cent.) admitted repeated gonorrheal infection; in 6 the blood serum had reacted positively. This appears to be of clinical significance. The number of patients without a history of lues but having positive Wassermann reactions was 9 (40 per cent.). Of the 23 cases 17 (74 per cent.), showed positive initial Wassermann reactions in the blood serum. Three of the operatively demonstrated cases in the earliest series antedated the use of the serological test, but responded definitely to the antispecific treatment. A provocative reaction was obtained in several instances. Of the 6 female patients, all of whom were married, the disease was admitted by 2, and a premarital infection was noted in 2 others. In the case of the remainder no history was obtainable, and it is most probable that they were infected after marriage. One before marriage had given birth prematurely to a syphilitic fetus. Four reported sterility, single or repeated spontaneous abortions and tendency to amenorrhea. All were childless except 1 and this one had had two miscarriages before the birth of a healthy child. Of the married male group, several reported that their wives had had miscarriages, 2 had healthy children, and the remainder were apparently sterile.

Time of Onset of Symptoms After Infection. Definite data bearing on this feature were obtainable in 16 cases. The earliest onset was 1 year, the latest 28 years, after the disease was con-

tracted. Only 3 gave evidence of the gastric malfunction attributed to the lesion present within the 5-year period, 6 between the 5 and 10-year period, and 7 between the 10 and 20-year period. The average was 11 years.

Duration of Symptoms. The shortest duration of the symptoms on admission was 7 months, the longest 7 years. Two-thirds fell within the 2-year period. The average duration was 3+ years. In striking contrast to this is the time-element in the benign ulcer group which so uniformly averages about 12½ years. The significance of such a brief clinical course, in view of the extensive pathological changes and altered chemistry having such direct diagnostic and prognostic bearing will be referred to later.

Clinical Course. In 9 cases the course was continuous from the outset, beginning abruptly with pain and vomiting in 2 instances, definitely intermittent in 4; intermittent, remittent or irregular in the remainder, but becoming continuous in the latter group after an average of 10 months. A distinctly progressive course was characteristic in 20 cases (90 per cent.).

Significance of Clinical Symptoms. Pain. Almost invariably the pain was described as situated in the epigastrium or pit of the stomach; in 1 instance, however, it was felt in the left hypochondrium. Dorsal radiation was noted 4 times. In 9 instances (39 per cent.) the pain was characterized as a distress; in 6 (26 per cent.) as cramping or severe; and in the remainder as dull or gnawing. In three-fourths of the cases the pain ensued immediately after eating and its duration was variable. In 4 cases it was continuous and made worse by alimentation. Definite nocturnal pain was evident in 3 cases only. In the uncomplicated gummatous ulcer-type, the pain-features simulated those of benign ulcer, being intermittent, rather periodic and delayed in appearance after meals from 1 to 3 hours. It differed from benign gastric ulcer in that anacidity was present and the pain was either only slightly relieved or not relieved at all by food or alkalies. The scirrhus or infiltrated types were associated with pain immediately after eating, which continued until the stomach had emptied itself. Such patients, to avoid discomfort, ate semisolid or liquid foods frequently and in small amounts.

Nausea. Noted definitely in only 3 instances: transient in cases with retarded motility or stenosis or associated with acute seizures.

Vomiting. This second most important symptom was noted in 19 cases (83 per cent.), and in 10 was present from the outset. In 4 cases retained gastric contents were vomited although in lesser amount than in cases of benign obstruction.

Hematemesis and Melena. Recorded in only 1 instance: single hemorrhage by mouth of 1 liter of blood. In fairly authentic cases

reported in the literature, however, severe and even fatal hemorrhages have occurred.

Flatulency. Definite complaint in 65 per cent., and present mainly for a period of one hour after taking food.

Bowel Function. Marked constipation in 50 per cent.; moderate to normal in 30 per cent. Constipation alternating with diarrheal movements in the remainder, but the former predominating.

Appetite. Characterized as good in 60 per cent.; abnormal in 10 per cent. (owing to starvation); complete anorexia or "poor" in 15 per cent.

State of Nutrition. All the patients showed marked loss in weight, over 50 per cent. having lost between 50 to 75 pounds. However, the degree of cachexia and diminished strength was mild and out of proportion to the loss in weight. This condition is converse to that which usually obtains in gastric malignancy.

Blood Estimation. Of 14 patients examined the average hemoglobin percentage was 80, average red count, 4,640,000, average white 5400.

Results of Abdominal Examination. Definite tumor or mass was absent in 20 cases (90 per cent.) and present in 1 instance (4 per cent.). In 2 cases (9 per cent.) there was a suggestion of "ridge-feel," and in all, muscle-resistance with marked or moderate tenderness. Visible peristalsis was absent in the retention cases on brief observation. Several instances are on record in which palpable epigastric tumor possessing the physical characteristics and mobility of a tumor of the stomach were associated with a history of infection and positive Wassermann reaction. However, our own inability to definitely determine that this tumor had its origin in the stomach, by all the clinical and roentgenological methods at our disposal, made it necessary to eliminate these from our series, in spite of the fact that such tumors disappeared under salvarsan and other antiseptic therapy. Hausmann has pointed out that undoubtedly it has been often erroneously assumed without more definite proof that such tumors were gastric tumors; that gumma of the liver tied off by cicatrizing contraction, or diffuse syphilitic liver-tissue tied off by cicatrized gummatous tissue may simulate tumor of the stomach.

Significance of Gastric Analysis. All of the patients, with the exception of one, who refused the tube, underwent the test. The extract usually showed poor chymification, especially that of the anacid cases, and was below normal in amount. The mucus content was not remarkable.

The small amount of gastric extract recovered in most cases was explained by the pathological conditions present. The number of patients with achylia was 18, or 82 per cent. of those examined. Four had an average of 22 per cent. free hydrochloric acid; the

average total acidity was 36 per cent. In two of these cases, achlorhydria alternated with a low hydrochloric acid content. Hypersecretion was not noted even in the retention cases which numbered 6 (26 per cent.). Blood was found in the gastric extract in 25 per cent., and occult blood was present in the feces of 17 per cent. of those examined. Lactic acid and sarcines were noted in 2 of the retention cases; in one of these Oppler-Boas bacilli were demonstrated.

A consistent achylorhydria, in fact, achylia, seems almost exclusively characteristic of luetic gastric disease. Special study has been made of gastric chemistry in syphilis of the stomach by Barbier, Robin and others, but to date no definite conclusions have been reached, owing to the variable findings. In the majority of cases in which the diagnosis was verified by postmortem examination or through the study of resected specimens the gastric analyses reported by many competent observers showed absence of free and combined hydrochloric acid. The pathology ranged from circumscribed gummatous ulcers with or without stenosis to diffuse infiltrated and contractured types. On the other hand, fairly convincing case reports by recent contributors to the subject showed the presence of free acid in normal or subnormal amounts. It is reasonable to presume that the extent and the situation of the local involvement and the systemic influence of the syphilitic virus are factors determining the gastric chemistry. However, the preponderance of evidence favors marked reduction of the gastric secretion, either through inhibition of the function of the gastric glands or atrophy of the mucous membrane. This probably has its inception in a gastritis granularis which may be a manifestation of the secondary or tertiary stage, as the direct or indirect result of the infection. Virchow recognizes an acute syphilitic gastritis which appears in the form of inflammatory infiltration, reddening of the mucous membrane, swelling, etc., and which belongs to the secondary stage. Chiari has described a diffuse and gummatous gastritis as belonging to the congenital form. In gross gastric lesions the more or less diffuse gummatous infiltration of the submucosa which finally extends to the mucosa or the diffuse syphilitic infiltrated type would at an early period affect gastric secretion. An atrophic mucosa was characteristic of all our microscopic sections. Neugebauer recently made a study of the gastric contents of 200 syphilitic recruits. Sixty-two per cent. of them were in the secondary stage and all showed definite subacidity. In 17 per cent. there was complete absence of hydrochloric acid or mere traces. Brugsch and Schneider in a review of the gastric chemistry of 100 tertiary syphilitics conclude that the frequency of achylia in tertiary syphilis in all probability is due to a chronic gastritis, and that a benign gastric ulcer in the presence of systemic tertiary syphilis is

associated with diminished secretion of hydrochloric acid. The argument has been advanced that the absence or reduction of the hydrochloric acid and ferments occurs only in advanced cases; that it is due to the rapid emptying of the gastric contents and involvement of the fundic glands, especially in the high contractured or hour-glass types. This explanation does not suffice because the same findings are present in early uncomplicated cases. Moreover, the results of my observations on acid values in benign and even malignant hour-glass stomachs, in which similar mechanical conditions surely obtain, would further seem to controvert such assumption.[19] Hausmann, who has made a critical study of 5 cases under his personal observation, regards anacidity as characteristic of syphilis. After reviewing 135 cases reported in the literature, he feels justified in considering as doubtful those cases with normal or increased secretion, and especially those incompletely studied. Patella,[20] in a review of the 140 cases of gastric syphilis he has found on record, states that the chemistry of gastric secretion was studied in only 11; in 9 of these there was anacidity, and achylia was noted in the cases especially examined. Clark,[21] in one of the more recent contributions to the subject, emphasizes the importance of gastric achylia and absence of free hydrochloric acid.

Significance of Pathology. All the cases showed deformity of variable degree, usually quite marked, with a reduction in size and contour. This was primarily the result of multiple cicatrizing gummatous ulcers or of areas of proliferative infiltration, circumscribed or diffuse, in association with perigastric adhesions. The degree of involvement was invariably in direct ratio to the duration of infection and gastric disturbance. In 4 of the 10 surgically verified cases there was definite hour-glass deformity. One patient had a stricture at the cardia, at the mid portion and at the pylorus. In all the cases the pars pylorica was the most extensively involved, although in 5 instances the involvement extended up both curvatures to the esophageal opening. In addition there was marked thickening and stiffness of the walls. The roentgenograms of two others showed hour-glass contraction, the greater loculus being above. In three instances, the ulceration and thickening seemed confined mostly to the posterior wall. In one of these cases the stomach was described as having a ruffled appearance due to the presence of multiple cicatrizing gummatous ulcers.

Grossly, there is no characteristic which readily enables the clinician to differentiate this form from some types of scirrhus carcinoma, linitis plastica, or sclerotic inflammation secondary to benign ulcer. Sailer[22] has recently called attention to this fact. The final diagnosis often rests with the exploratory laparatomy or the postmortem. However, the latter two forms are quite rare.

Microscopically, the appearance of the tissue is unlike that of

benign ulcer or carcinoma. There is usually marked atrophy of the mucous membrane, hypertrophy of the submucosa, and a thickened muscularis owing to a dense connective-tissue infiltration or fibrous hyperplasia. It is quite evident from the microscopic sections that the alteration in structure and function of the gastric mucous membrane is caused partly by a disturbance in the blood supply. The bloodvessels are invariably obliterated; in addition there is a general contracture of the surrounding tissue, the result of marked fibrosis of the submucosa and muscularis (Figs. 3d, 7a, 7b and 7c). This thickening of the submucosa and muscularis somewhat simulates linitis plastica, but everywhere there is evidence of an obliterative endarteritis and perithelial lymphocytic infiltration which is the most characteristic feature of syphilitic tissue. Although the spirochetes have been demonstrated in congenital syphilitic tissues, we were unable to find them in these acquired cases.

Gross filling defects, mainly in the lower two-thirds, suggesting extensive disease or involvement were readily apparent in the other roentgenograms. The congenital case showed a small deformed stomach, the normal portion reduced to a sac at the cardia. To the roentgenologist, the combination of gross filling defect, tendency to hour-glass deformity, absence of palpable mass and six-hour barium residue, and the absence of a proportionate cachexia, suggest gastric syphilis. Technically, however, such findings cannot be differentiated from carcinoma.

The association of syphilitic lesions or their sequelæ in other parts of the body is added proof of the specific nature of the gastric lesion. In this respect, aortitis, aneurysm and gummata of the liver or hepar lobatum were noted in several instances. Lesions of the skin and mucocutaneous junctions, hyperplasia of the lymph nodes, tibial periostitis, degenerating gumma of the chest wall, and late gummatous meningitis, were also present in individual cases. Symmers,[23] in recent postmortem studies of 314 cases of late acquired syphilis, noted the frequency of interstitial orchitis and indurative atrophy of the base of the tongue. Such instances have not been recorded in this series.

Results of Operation and Treatment. Of 10 patients operated on we were unable to get reports from 2. Three (13 per cent.) were cured and 5 (22 per cent.) were much improved. All these patients received antisyphilitic treatment in addition.

Of 13 patients not operated on, reports have been received to date from 12. Two (9 per cent.) are cured, 8 (35 per cent.), are much improved, and 2 are not improved. The total cured and improved number 16 (69 per cent.). This result exceeded expectations and is encouraging. Thorough treatment instituted during the exudative stages gives brilliant results. Advanced cases often require surgical interference because of stenosis or hour-glass deformity, the result of cicatrization or fibrous hyperplasia. If the involvement

is extensive, the result of even combined surgical and specific treatment may be disappointing. The desideratum is early diagnosis and intensive treatment.

SUMMARY AND CONCLUSIONS. 1. Syphilis of the stomach, though rare, is not as infrequent as is generally supposed. The aid of the Wassermann-Noguchi reaction and roentgen rays are necessary to establish the presence and the specificity of the lesion.

2. Denial of the disease, lack of evidence pointing to a primary lesion, or absence of positive Wassermann reaction does not exclude the possibility of gastric syphilis.

3. The diagnosis is based on a history of infection, a consistent positive Wassermann reaction, undisputable evidence of a gross gastric lesion, and—excluding cases showing irreparable extensive disease—a permanent cure by purely antisyphilitic measures. The diagnosis is often accidental. The possibility of syphilis should be considered in every atypical case, or in those not responding to ordinary methods of medical management.

4. The symptomatology which is fairly characteristic of gastric syphilis in view of the cases reported herewith, is suggestive of benign gastric ulcer; the gastric chemistry and roentgen findings rather suggest carcinoma. The average age of patients with acquired syphilis of the stomach is about 35; the duration of the complaint averages 3 years. In most instances the condition is characterized by an initial intermittent course, followed soon by continuous symptoms and associated with epigastric pain of variable degree, felt shortly after taking food and not relieved by food or alkalies. From the outset there is a tendency toward emesis, a variable degree of flatulency, good appetite, infrequency of hemorrhage and palpable tumor, diffuse abdominal resistance, a progressive course, and marked loss in weight without cachexia.

5. Anacidity or achylia is characteristic of the majority, if not of all, cases of actual gastric syphilis. This can be explained by the influence of the pathological process upon the gastric mucous membrane.

6. Extensive gastric involvement is frequently present at the time when gastric disturbance first becomes manifest.

7. A gummatous ulcer, usually multiple, and especially a diffuse syphilitic infiltration with variable degree of contracture (fibrous hyperplasia), thickening, deformity, and perigastric adhesions chiefly involving the pyloric segment, is the usual pathological condition. Demonstration of the presence of Spirocheta pallida in the resected tissue would be final proof of specificity.

8. Results from antispecific treatment are encouraging in all but very advanced cases. Surgical interference is indicated in certain cases. Early diagnosis and intensive treatment invariably result in symptomatic cure and structural improvement.

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FIG. 1.—(108061) No retention from the six-hour barium motor meal. Hour-glass stomach. Roentgen diagnosis: Syphilis or ulcer of the stomach.

Male, aged 34 years. Genital chancre, skin and mucous membrane secondaries 20 years previously. Gonorrhea three times. Gonorrheal arthritis. Chronic urethritis. Moderate alcoholism. Gastric disturbances 2 years. Cramping epigastric pains promptly after meals. Nausea and vomiting. Appetite fair. Loss of weight, 51 pounds. Liver and spleen palpable. Wassermann 3 plus. Achylia. Intravenous salvarsan four times. Mercurial inunctions and iodids. Treatment was begun July, 1914. January 5, 1915, symptomatically cured with a gain of 60 pounds. February 2, 1915, Wassermann 3 plus.

FIG. 2.—(94691) No retention from the six-hour meal. Stomach small, showing high hour-glass constriction with marked narrowing and irregularity of the pars media and pars pylorica.

Male, aged 37 years. Syphilis 9 years previously. Gastric symptoms 3 years. Epigastric pain promptly after meals, lasting one hour or longer. Continuous complaint with brief periods of remission. Pyrosis, flatulency. Loss of weight, 35 pounds. Appetite good. Wassermann 3 plus. Hyperplasia of cervical glands, epigastric resistance and tenderness. Total acids 4, no free HCl. Intravenous neosalvarsan, six times. Markedly improved. Gain of 30 pounds.

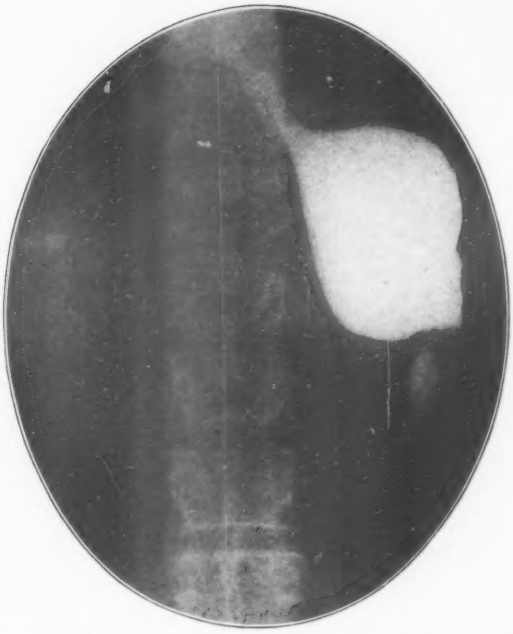

FIG. 3a.—(92014) Retention of one-fourth the six-hour barium motor meal. High hour-glass constriction. Reflux of the meal into the esophagus.

Male, aged 33 years. Syphilis 7 years previously. Symptoms 3 years. Epigastric discomfort due to sense of fullness and heaviness immediately after meals. Generous meal induces pain; emesis necessary for relief. Liquid diet for past 2 years. Recent vomiting of retained food material. Wassermann, total inhibition. Achylia. Salvarsan and mercury caused symptomatic improvement, but moderate pyloric obstruction persisted. Operation advised and accepted.

FIG. 3b.—(92014) Resected gross specimen. Macroscopically, the resected pyloric portion of the stomach presents a smooth uniform mucosa with three small superficial erosions. Gross section shows marked thickening of submucosa and muscularis.

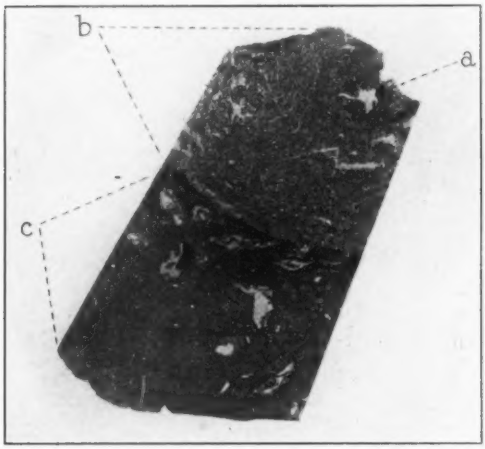

FIG. 3*c*.—(92014) Section of tissue from stomach magnified 4 times. *A*, atrophic mucosa, curling due to fixing solution; *B*, hypertrophied submucosa; *C*, thickened musculature.

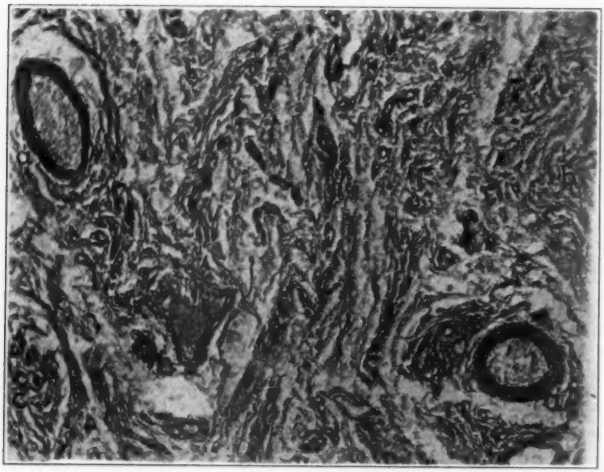

FIG. 3*d*.—(92014) Microphotographic section, magnified 100 times, of tissue from stomach. *A*, bloodvessels with thickened walls; *B*, dense connective tissue; *C*, nest of phagocytes. No evidence of cancer.

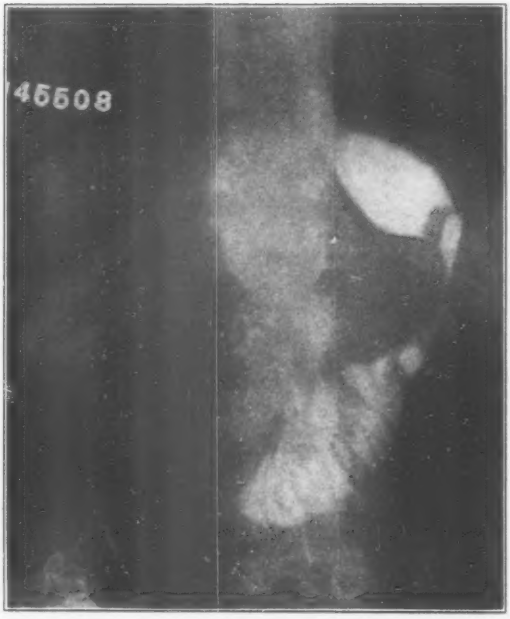

FIG. 4.—(145508) Stomach small, showing high hour-glass. Marked narrowing and irregularity of the pars media and pylorica. Pylorus gaping. No retention. Reflux of the meal into the esophagus.

Male, aged 25 years. Congenital syphilis. Exploratory operation on stomach 3 years previously. Gastric disturbances of 7 years' duration. Progressive course. Liquid or semisolid foods taken at frequent intervals. Regurgitation. Solid foods cause pain and emesis. Loss of weight 95 pounds. Numerous stigmata. Filtrate, 50 c.c.; achylia.

FIG. 5*a*.—(58949) Two views; First examination May 22, 1914. Roentgen examination negative.

Female, aged 27 years. Syphilis not admitted. Later it was learned that the husband was being treated for lues. Two miscarriages, one apparently healthy child. Gastric symptoms present 1½ years. Dull, heavy epigastric distress immediately after meals, lasting 10 to 15 minutes. Two or three hours later, intermittent, sharp epigastric pains radiating through to back. Quantitative food distress. Occasional emesis; flatulency, anorexia, weakness, costiveness, loss of weight. No hemorrhages. Hyperplasia of cervical glands, degenerating gummata in the region of the fifth right costo-chondral and right sterno-clavicular articulations. Total inhibition hemolysis.

FIG. 5*b*.—(58949) Second examination August 31, 1914. No retention from the six-hour meal. Pylorus gaping. Narrowing of the pars media and cardiaca. Roentgen diagnosis: Lesion of the stomach.

Achylia. Wassermann persistently positive after repeated intravenous injections of salvarsan; but there was marked general improvement by November, 1915.

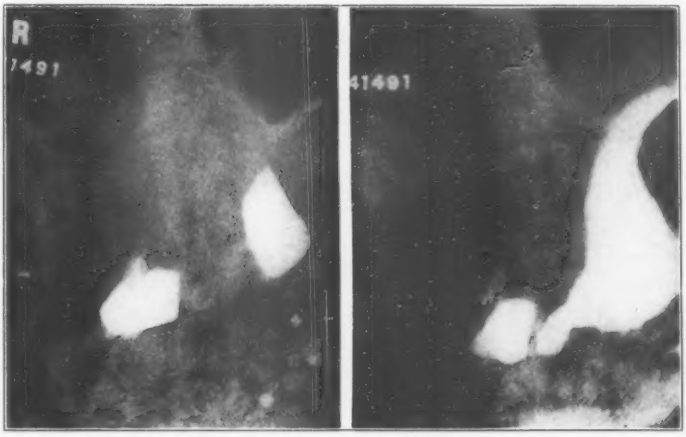

FIG. 6*a*.—(141491) Two views: September 11, 1915. No retention from the six-hour barium motor meal. Filling defect pyloric end of stomach with no corresponding palpable mass.

Female, aged 30 years. Married 3 years previously. Formerly a London barmaid. Genital chancre and oral mucous membrane secondaries about ten years previously. Two years later gave premature birth to viable syphilitic child. For one year weekly hypodermics of mercury salicylate and "pills" for two years. Gastric complaint of 8 months' duration prior to examination; epigastric discomfort soon after eating (eased by soda), even after partaking of a small meal. Gastric analysis by a local physician at outset showed absence of HCl. The acid prescribed disagreed and was voluntarily discontinued. Daily complaint. Appetite excellent. "I could eat all the time." Fresh fruits and soups seemed to agree. Chronically constipated; becoming worse. Ate small amounts frequently, but loss of weight was progressive; altogether 46 pounds. For the past month forced to vomit to relieve distress attributed to gas. Every third day regurgitation of small amounts of bitter-green fluid. Absence of diarrhea or unusual nocturnal pain (clinical signs of contracted stomach. Good color; hemoglobin 80 per cent. Epigastric resistance, but no palpable mass. Heart, lungs, etc., objectively negative. Wassermann reaction, total inhibition of hemolysis. Spinal fluid reacted negatively.

FIG. 6*b*.—(141491) Second roentgenogram taken November 27, 1915, shows marked improvement.

After the seventh intravenous salvarsan injection, and a three months' course of mercurial inunctions and potassium iodid, the reaction was strongly positive. Repeated gastric analysis showed persistent absence of free HCl; absence of peptic activity (Mettes' method) even after dilution of filtered gastric contents with $\frac{1}{2}$% normal HCl in proportion of 1 to 16. Average total acidity, 9. Symptomatically well after third intravenous salvarsan treatment. Treatment was begun September, 1915. Patient discharged as cured January, 1916. Gain of 35 pounds. Present health (May, 1916) excellent. Further antispecific treatment recommended.

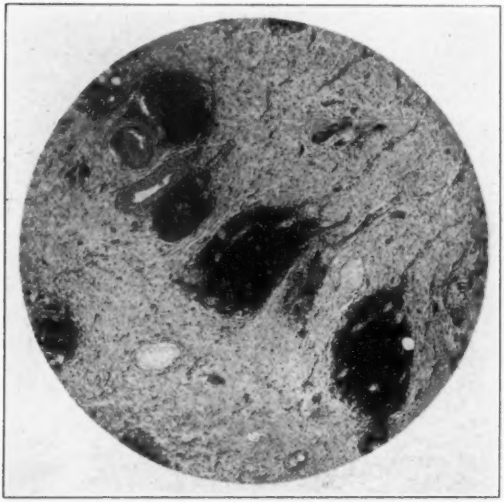

FIG. 7*a*.—(68261) Multiple groups of lymphocytes and marked fibrosis of submucosa.

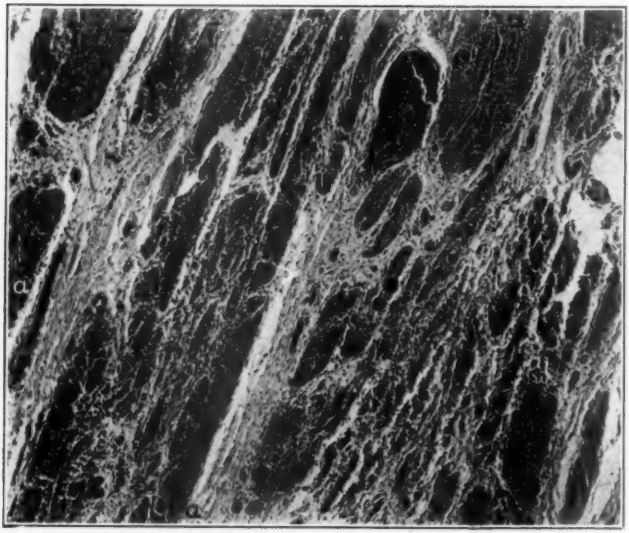

FIG. 7*b*.—(68261) (*a*) Marked fibrosis of gastric musculature.

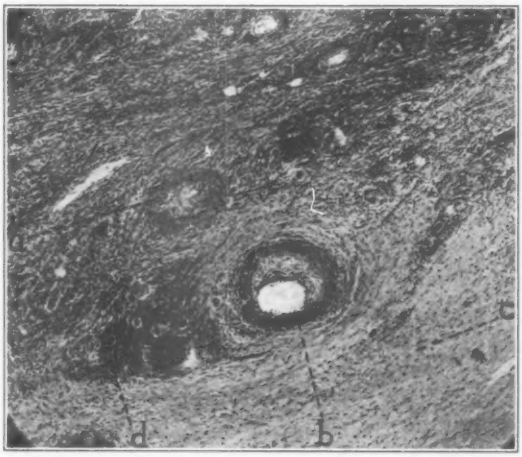

FIG. 7*c*.—(68261) (*a*) Obliterated bloodvessel; (*b*) partially obliterated bloodvessel; (*c*) fibrous tissue; (*d*) group of lymphocytes.

Male, aged 43 years. Lues 16 years' duration. Treated for 2 years. Gastric symptoms for 2 years and 3 months. At the outset at frequent intervals had "spells" lasting 3 or 4 days; left epigastric pain 15 to 20 minutes after meals lasting about a half hour. Trouble gradually progressive and daily pain becoming severe; also pyrosis and emesis. Acute pain seizures may last 2 to 6 hours. Absence of hyperacidity and stasis. Loss of 20 pounds in weight.

Upper abdominal resistance, tenderness in lower left epigastrium and no palpable mass. Anacidity. Preoperative diagnosis, carcinomatous gastric ulcer. On June 3, 1912, exploratory operation (W. J. Mayo): "Ulceration and thickening (3 x 3¾ cm.) on the posterior wall of the pyloric portion. Remainder of stomach above was small and hypertrophied. Syphilitic appearance." A partial resection was done. Wassermann reaction, after laparotomy, was strongly positive. Antisyphilitic treatment was given with marked improvement.

INTERMEDIARY METABOLISM IN DIABETES.

By Graham Lusk,
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The phenomena of human life are dependent upon the reactions which take place between myriads of cells and their food and oxygen supply. One kilogram of body substance contains 30 grams of tissue nitrogen. The essential waste of this nitrogen amounts to 1.7 mgs. per kilogram of body substance per hour, or one part in 18,000 of that which is contained in the body. This is the wear and tear metabolism of protein at a minimal level. One may calculate that the least amount of energy which is necessary to maintain the life processes of 1 kg. of body substance is 1 calorie per hour, which represents the quantity of energy contained in 215 mgs. of glucose. It has been estimated that 1 kg. of body tissue contains cells having a total surface area of 150 square meters. Therefore, when each square meter of this cell surface is supplied with a sugar solution containing 1.5 mgs. of glucose per hour, the life of the tissue can be maintained. One can imagine how thin a film of glucose solution around the cell is necessary for the maintenance of its life. In ordinary daily life, two-thirds of the energy which supports our bodies is derived from glucose. In diabetes the power to oxidize glucose is lost. It may be interesting to inquire into the nature of the process of the oxidation of glucose.

There are two biological reactions of glucose which have long been known under the heads of lactic acid and alcoholic fermentation. In the first instance a molecule of glucose containing six carbon atoms is broken into two molecules of lactic acid, each containing three carbon atoms. In the second instance a molecule of glucose liberates two molecules of alcohol, each containing two carbon atoms and two molecules of carbon dioxide. Both of these transformations are anaërobic; that is to say, they do not require oxygen for their production.

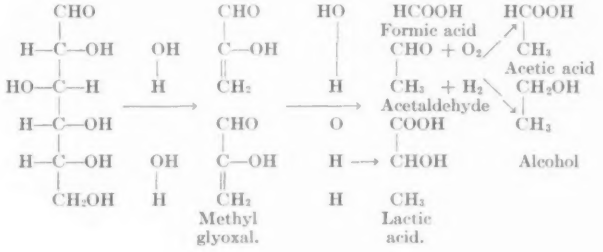
Lobrey de Brun and van Eckstein found that when glucose solutions contained even traces of hydroxyl ions, this alkalinity served to transform optically active glucose into a mixture of a multitude of other sugars, a mixture which did not rotate polarized light. This phenomenon was called mutarotation. Nef stated in 1907 that any ordinary hexose (such as glucose, fructose, galactose) when treated with weak alkali can yield in theory 116 different substances. Of these, he was able to identify 93, of which 47 were different forms of sugar, and the rest, different fragments of sugar cleavages. L. J. Henderson finds that a glucose solution undergoes mutarotation when the alkalinity of the solution is the same as that of the blood.

The presence of traces of acids prevents all these transformations. That this may have biological significance is suggested by the work of Rona and Wilenko, who found that a decrease in the alkalinity of a perfusing fluid greatly reduced the utilization of glucose by an excised, beating heart. They suggested that the diabetic condition is the outcome of a slightly acid reaction within the cells. The biological chemical reactions of sugar in the organism may be best explained by assuming that sugar is first dissociated into substances containing three atoms of carbon, such as methyl glyoxal or glyceric aldehyde. It is but a step to convert such fragments into either lactic acid or into alcohol; or to oxidize them; or by synthetic reunion to convert them into sugar once more. In the body the synthetic reunion always takes the form of glucose. After this fashion one can understand how levulose (fructose) may be transformed into glucose in the diabetic organism by the union of two intermediary substances, each containing three carbon atom chains.

Dakin, Neuberg and others have produced evidence which indicates that methyl glyoxal is an important intermediary product in sugar metabolism. Methyl glyoxal is a substance which in asphyxial conditions is readily converted into lactic acid. Biologists find that lactic acid is not oxidized. On the other hand, methyl glyoxal in the presence of oxygen readily undergoes decomposition. Neuberg has shown that the yeast cell may produce acetaldehyde from it, and that this may then be reduced to alcohol. In the presence of oxygen, however, acetaldehyde may be converted into acetic acid, which can readily be oxidized in the body into carbon dioxide and water.

The provisions in this scheme of glucose metabolism are such that if asphyxial conditions are encountered, lactic acid is produced (which may be reconstructed into glucose). Under asphyxial conditions acetaldehyde does not arise in the tissues, for if it did arise in the presence of asphyxia, alcohol would then be a product of metabolism. The prior formation of lactic acid, therefore, automatically prevents the organism from becoming a brewery.

These relations are set forth in the following formula:



In diabetes the glucose molecule appears to be invulnerable. If lactic acid or methyl glyoxal are administered they are completely transformed into glucose. If in diabetes the muscles be rendered asphyxial, by means of strychnin convulsions, no lactic acid arises from glucose, as occurs in a normal animal, which indicates that no methyl glyoxal is formed. It is conceivable, however, that after giving fructose to a diabetic animal during strychnin convulsions, some of the dissociated three carbon atom chains which are usually transformed into glucose might produce lactic acid. In complete diabetes, however, fructose is limited in its breakdown to chains of three carbon atoms, which are then convertible into glucose. The phenomena of the mutarotation of sugars in diabetes follows only one direction, and that leads to transformation into a single end product, glucose.

By the same method glucose is formed from protein. In the metabolism of protein, chains containing three carbon atoms are liberated in the organism, and these may be synthesized into glucose. The amino-acid alanin affords the simplest expression of this reaction. Alanin on hydrolysis is converted into lactic acid,

$$CH_3CHNH_2COOH + HOH = CH_3CHOHCOOH + NH_3$$

and, as shown above, lactic acid is convertible into glucose. A full analysis of these conditions has elsewhere been attempted.[1]

It has been established that in a fasting, meat-fed dog rendered completely diabetic by phlorhizin, there is a constant relation between the number of grams of urinary nitrogen and of urinary glucose. This relation is, Dextrose : Nitrogen = 3.65 : 1—and is commonly called the D : N ratio. Since 1 gram of urinary nitrogen represents the destruction of 6.25 grams of protein, it follows that 3.65 grams of glucose must have arisen from the metabolism of 6.25 grams of protein, or 58 per cent. of the molecular complex. It is well, perhaps, to place on record that this relation has been established for a man (a cancer patient) under the influence of phlorhizin and for severe types of diabetes mellitus. The following table verifies this statement, the D : N ratios being given in successive day-to-day periods:

D : N Ratios.

	Phlorhizin.		Diabetes mellitus in man				
	In dog.	In man.					
Author.	Lusk.	Benedict, S. R.	Mandel and Lusk.	Greenwald.	Foster.	Mosenthal.	Joslin.
	3.65	3.58	3.60	3.75	3.58	3.75	3.69
	3.66	3.82	3.65	3.56	3.38	3.85	3.67
	3.62	3.66	3.66	3.70	....	3.44	3.67
	3.64	3.68	3.64	3.64	3.48	3.66	3.68

[1] Lusk, Elements of the Science of Nutrition, third edition, 1917 (in press).

It may be stated, without qualification, that sugar does not arise from the metabolism of fat in the organism.

In complete diabetes the patient is, therefore, thrown upon the energy content of fat and of those fragments of protein which do not pass over into glucose for the maintenance of his life.

That this is true may be further verified by examining the respiratory quotients obtained in diabetes. It will be remembered that when glucose is oxidized in the organism, one volume of oxygen is inspired for each volume of carbon dioxide expired and the respiratory quotient is unity. When protein is oxidized the respiratory quotient is 0.8 and fat yields a quotient of 0.707. But when glucose arising from protein cannot be oxidized the respiratory quotient of protein falls to 0.63. The respiratory quotient in severe diabetes will, therefore, fall below that of fat. As a matter of fact, results have been obtained which show that the quotient observed in severe diabetes is about 0.69. The calculated "non-protein respiratory quotient" is obtained by deducting the influence which the protein metabolism would have exercised upon the observed respiratory quotient. This is found to be about 0.70 instead of 0.707, the theoretical value of fat. The "non-protein respiratory quotient" would have been higher than 0.707 if glucose had been oxidized with fat. Since the analytical methods do not allow of an accuracy greater than 1 per cent., it may be deduced that the severe diabetic subsists upon fat and those fragments of amino-acids which do not form glucose.

These results appear in the following table:

	D : N.	Respiratory quotient.	Non-protein respiratory quotient.
Phlorhizinized dog	3.54	0.687	0.704
Diabetic man (G. S.)	3.50	0.697	0.700
Diabetic man (C. K.)	3.97	0.687	0.699

It may be added that the formation of β-oxybutyric acid in the oxidation of fat likewise tends to depress the respiratory quotient unless this effect is compensated for in the expulsion of carbon dioxide from its union with bicarbonate of soda.

The heat production in diabetes does not vary greatly from that found in health unless an increased protein metabolism instigates a higher oxidation. The metabolism in severe diabetes is, therefore, finely adjusted and follows known biological laws.

THE CLINICAL SIGNIFICANCE OF THE GLUCOSE : NITROGEN RATIO IN DIABETES MELLITUS.

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PART I.—THEORETICAL AND EXPERIMENTAL.

Review of Previous Studies on the Glucose : Nitrogen Ratio. From the time it was recognized that sugar arises in the organism from protein, the relation of carbohydrate to protein metabolism has become of importance in the study of diabetes. If the maximal production of glucose from protein in total diabetics could by any means be ascertained, it is evident that a gauge of the severity of this disease would thereby be afforded. As the nitrogen of the urine is chiefly produced from albuminous substances, which also form glucose, it follows that this important question might be attacked through a study of the relation of the urinary glucose in the diabetic subject to the nitrogen elimination. Such is the reasoning underlying the large number of researches on the so-called G : N ratio[1] in diabetes.

The theory itself here involved is, however, open to question. The urinary glucose of the human diabetic, as pointed out by von Noorden,[2] cannot be certainly regarded as all which can be possibly produced within the diabetic organism, but rather only that portion of the total amount of carbohydrates escaping utilization or storage. Likewise the nitrogen of the urine may, as argued as early as 1901 by Umber,[3] by no means represent all that arises from protein katabolism, for a portion of the nitrogen so liberated may fail of excretion in the urine through its being utilized in the synthetic processes of intermediary metabolism. Still another criticism of the utility of the G : N ratio has been previously mentioned by Janney and Csonka.[4] The total amount of urinary nitrogen cannot be properly regarded as arising exclusively from sugar-producing protein. It seems then, with justice that up to the present the G : N ratio has not been regarded by clinicians as of much practical value in the treatment of diabetes.

Quite aside, however, from such theoretical objections the results of previous experimental studies on this subject present a confusing picture. Various attempts here have been made to ascertain the maximal glucose production in diabetics by means of

[1] Noorden, C. v. Handbuch d. Path. d. Stoffwechsels, Berlin, 1907, ii, 33.
[2] Handbuch d. Path. d. Stoffwechsels, Berlin, 1907, ii.
[3] Ther. d. Gegenw., 1901.
[4] Jour. Biol. Chem., 1915, xxii, 203.

experiments in which proteins were administered with control of the diet. Such experiments by Rumpf, Rosenquist, Mohr and a number of others[2] have led to surprising divergent results, for they apparently show variations in the urinary G : N ratio from 0.01 : 1 to 12 : 1 or even more. Von Noorden accepts 5 : 1,[5] elsewhere 4 : 1[6] parts of glucose excreted to 1 part of nitrogen as representing maximal glucose formation from protein. The criticisms, however, which annul the value of such experiments are numerous. As they have been already discussed recently by the writer,[7] they need not be restated here.

A way out of such uncertainty seemed at first afforded by observations made on the fasting depancreatized dog, which shows a fairly constant urinary G : N ratio averaging 2.8 : 1. From this value Minkowski has calculated that about 45 per cent. of body protein is convertible into glucose. However, in another form of diabetes, that produced by phlorhizin in the dog, the G : N ratio of 3.65 : 1, corresponding to the production of 56 per cent. of glucose from protein, has been established by Lusk. Janney and Csonka,[4] on the basis of much more numerous experiments than those available to Lusk at the time of his publications, lately demonstrated that 3.4 : 1 is the more exact average fasting ratio for the phlorhizinized dog. Making due deductions for urinary nitrogen present in or originating from non-glucogenetic substances, these authors calculated that 58 per cent. body protein as a maximum can be converted into glucose. That Lusk making use of the higher ratio 3.67 : 1 also computed the almost identical glucose yield, 58.7, is to be explained by the fact that he used the uncorrected nitrogen values. If Janney and Csonka's method of calculation be employed with the 3.67 : 1 quotient, the result is an apparent glucose formation of 62 per cent. from protein. That this value is too high has been demonstrated by direct feeding experiments, to be alluded to later in this article.

Phlorhizinized animals belonging to other species, however, show strangely enough the 2.8 : 1 G : N quotient. As no adequate explanation has ever been advanced for the occurrence of both these high and low ratios in the same kind of diabetes, the actual significance of the urinary G : N ratio and also the maximal extent of glucose formation from protein has remained in doubt.

Establishment of the Glucose : Nitrogen Ratio in Complete Diabetes with the Help of Improved Methods. Evidently a new angle of attack was required for solution of the problem of determining the maximal extent of sugar formation from

[5] Noorden, C. v. Zuckerkrankheit und ihre Behandlung, Berlin, 1912, 6th edition, 16.

[6] Noorden, C. v. Disorders of Metabolism and Nutrition, New York, 1905, Part VII, 79.

[7] Janney, N. W. Arch. Int. Med., 1916, xviii, 584.

protein in diabetes. This has been afforded by studies made in our laboratory during several years past. As the methods employed have been previously described,[8] but a few words need be added here concerning their principle. Fasting dogs made completely diabetic by phlorhizin show a remarkable regularity in nitrogen and glucose excretion. Sugar ingested within certain limits as to amount is eliminated quantitatively in the urine. By careful preliminary studies we found it possible to so refine the experimental conditions that the glucose originating from ingested food substances could also be quantitatively estimated. When such experiments are properly carried out the results are surprisingly uniform. Usually they show even in extensive series of individual experiments a maximal variation of 10 per cent. or less.

With the aid of this procedure, the subject of glucose formation from protein has been extensively investigated in our later work, which has grown to the extent of a hundred or more complete metabolic experiments. Protein and muscle of various origin were fed as indicated, and the total amount of glucose arising from these materials in the completely diabetic organism ascertained. By comparing the sugar so formed to the nitrogen previously estimated in the material fed it is possible to establish the actual relationship existing between the maximal amount of sugar arising from body and other proteins in diabetes and the nitrogen content of these proteins. Thus the real protein G : N ratio could be established which differs from the urinary G : N ratio discussed above.

This new experimental method was now put to a critical test. For reasons which cannot be here detailed, in phlorhizin diabetes the glucose excreted during a fast is known to be practically entirely of protein origin.[9] In view of this, if our feeding experiments led to trustworthy results and due allowance be made for that part of the urinary nitrogen which is unrelated to glucose formation, the same amount of glucose in proportion to nitrogen should be eliminated in the urine of fasting phlorhizinized dogs as the proteins of such animals yield when fed to other phlorhizinized dogs. In both cases our experiments demonstrated that almost the same amount of glucose was formed from body proteins, which result corresponds to the protein G : N ratio of 3.6 : 1. As it has been demonstrated that sugar ingested by these animals is quantitatively excreted it is evident from the identity of these results, both that phlorhizin diabetes is a complete diabetes and that the maximal amount of sugar is formed from proteins ingested by these animals.

The successful outcome of these experiments led us to extend them to the human species and the problems presented by diabetes mellitus. By feeding human muscle to our completely diabetic dogs as done previously, it could be finally shown that the maximal

[8] Janney, N. W. Jour. Biol. Chem., 1915, xx, 321.

[9] Lusk, G. Phlorhizinglukosurie, Ergebn. d. Physiol., 1912, xxii, 315.

sugar formation from the chief body proteins of man is again 58 per cent., corresponding as in the case of the dog, to the protein G : N ratio of 3.6 : 1, the nitrogen here being protein nitrogen of the human muscle. The maximal protein G : N ratio of other species, including the ox, fish, and rabbit, was found to be about the same as for dog or man. As no difference is known to exist between sugar formation from protein in human as compared to phlorhizin mellituria, it is justifiable to apply this result to the study of diabetes mellitus. Body proteins other than muscle were found also to yield so far as studied about 58 per cent. of glucose on an average under the same circumstances. The conclusion may, therefore, be drawn that the body proteins of man collectively yield in total diabetes about 58 per cent. of glucose corresponding to the protein G : N ratio 3.6 : 1.

This quotient cannot, however, be accepted without modification as representing the maximal fasting urinary G : N ratio in diabetes mellitus, for in the urine certain of the nitrogen, as we have seen, is not properly to be regarded as arising from sugar-forming protein. This value is, however, known, and the calculation based on direct experiment could thus be made that when the urinary G : N ratio ranges about 3.4 : 1 maximal diabetes mellitus is present.[10]

Through these experimental data and deductions it is believed that former criticisms of the value of the G : N ratio lose their weight. This quotient may then be regarded as a true indication of the severity of the disease. Diabetics during a fast or on a carbohydrate-free diet may be expected to exhibit urinary G : N ratios in the neighborhood of 3.4 : 1. A number of such cases have already accumulated in which the symptoms likewise indicated the severe type of diabetes.[11] The value of this index of the severity of diabetes is then emphasized by the clinical findings. It is likely that once general attention is turned in this direction the number of such cases reported will increase.

These studies are also of importance in the question of glucose formation from fat in diabetes. As all the glucose and no more than appears in the urine of fasting diabetic subjects can be accounted for in these experiments as originating from protein, it is evident that sugar formation from fat is not extensive. This corroborates the results of the most recent researches. This matter is, however, more of theoretical interest, and need not be more than alluded

[10] Janney, N. W., and Blatherwick, N. R. Jour. Biol. Chem., 1915, xxiii, 77.

[11] Mandel, A. R., and Lusk, G. Deutsch. Arch. f. klin. Med., 1904, lxxi, 472; Lusk, G., Jour. Am. Med. Assn., July 23, 1904, 241; Allard, E. I., Arch. f. Exp. Path. u. Pharm., 1907, xvii, 1; Foster, N. B., Deutsch. Arch. f. klin. Med., 1913, cx, 501; Greenwald, I., Jour. Biol. Chem., 1913–14, xvi, 375; 1914, xviii, 115; Geyelin, H. R., and Du Bois, E. F., Jour. Am. Med. Assn., 1916, lxvi, 1532; Allen, F. M., and Du Bois, E. F., Arch. Int. Med., 1916, xvii, 1010.

to in the present connection. In this paper the clinical applications of the data are of chief importance and are discussed in the succeeding paragraphs.

PART II.—PRACTICAL APPLICATIONS.

CLINICAL METHOD OF ASCERTAINING THE G : N RATIO. Following the original suggestion of Lusk,[12] most clinicians in studying the G : N ratio have put their patients on a carbohydrate-free high protein diet. This procedure is, however, open to objection. Anyone having experience with this classical diabetic diet is forced to the conclusion that its administration is both difficult and may lead to danger for the patient. Foster,[11] also Allen and Du Bois,[11] and others, have emphasized this point.

Aside from this consideration the utility of this method of establishing the G : N ratio is subject to a further criticism. The ingestion of large amounts of protein causes a considerable augmentation in the sugar and nitrogen elimination in the urine, which in many cases may confuse the results. In rare cases of complete intolerance to carbohydrate this effect is not so apparent for the following reason. Ingested proteins of various origin, as shown by the writer and his coworkers, give rise to an average glucose production of about 60 per cent. in the completely diabetic organism, which also yields through katabolism of its own protoplasm nearly the same relative amounts of urinary glucose and nitrogen. As a result the ingestion of even large amounts of protein in the food is accompanied by no obvious change in the G : N ratio when the diabetes is complete. This is most clearly demonstrated by Lusk's experiments.[13]

When, however, incomplete diabetes exists, as is the rule, conditions are different. A certain amount of body protein is broken down and a certain amount of the resulting glucose utilized, the remainder being eliminated. The same holds true for ingested protein. If, as may happen, the full glycolytic capacity of such a milder case of diabetes is reached when all glucose possible arising from the patients own proteins has been utilized, it is clear that more glucose in proportion to nitrogen is likely to be excreted in the katabolism of protein ingested by this individual than in the case of his body proteins. The fact that a certain amount of body protein is spared by the action of albumin and fat of the food adds further to the confusion presented by the analysis of this metabolic picture.

Allard's case[14] may serve as an example bearing on this point. A diabetic was put upon a meat-fat diet alternating with fasting days.

[12] Jour. Am. Med. Assn., July 23, 1904, 241.
[13] Reilly, F. H., Nolan, F. W., and Lusk, G. Am. Jour. Physiol., 1898, i, 395.
[14] See Allard's table, modified by Lusk, G., Arch. Int. Med., 1909, 1.

Usually the lowest G : N ratios were recorded during starvation and the highest on the meat-fat days. It is probable that only on the fasting days the actual G : N ratio of endogeneous source prevailed, and that the cause of more glucose in proportion to nitrogen being excreted on the food days is as just indicated.

The only recourse, then, remaining to us in seeking to ascertain the true G : N ratio is to order a complete fast. Fortunately Allen's careful researches have demonstrated this to likewise represent the best treatment for diabetics. The G : N ratio can then readily be obtained during the initial fast. All that is necessary is a careful exclusion of food, faithful collection of the twenty-four hour urine, and nitrogen determinations in addition to glucose. As the carbohydrates of the body may become eliminated and thus increase the glycosuria during the first days of the fast and the body's capacity to utilize sugar may also vary, it is necessary to make observations during a number of successive days, five if possible. The G : N quotient after a single day's fast has little real meaning. This has been emphasized by Joslin,[15] though other recent authors on diabetes tend to consider the observation of the fasting G : N ratio for very short periods of time to be of consequence.

Proper hospital facilities are, of course, practically requisite to ascertain this index of the severity of diabetes cases, but fortunately profession and public are more and more becoming alive to the fact the glycosuric patients should at least undergo a period of study in institutions properly equipped for their care.

Clinical Significance of the G : N Ratio. The G : N ratio properly established for fasting patients is a valuable aid in the study of diabetes mellitus. In general it may be stated that the more nearly the G : N ratio ranges about 3.4 : 1, the graver becomes the prognosis. From Allen and Du Bois's article[11] which appeared during the composition of the present communication, and also states similar conclusions, the following may be quoted in this regard:

"The occurrence of the dextrose-nitrogen ratio of the phlorhizinized dog in any human patient may be taken as a sign of the gravest immediate significance. The few known to have exhibited this ratio during fasting have died, except the patient of Geyelin and Du Bois." Conversely the more nearly the G : N ratio approaches 0 : 1 the more favorable in general is the prognosis.

There are, however, a number of factors to be considered in considering the prognostic value of this index. Important among them is the rapidity of the fall of the ratio during the fast. Persistence of a high G : N ratio over a number of days bespeaks great severity of the diabetic process but fortunately is rarely observed. Again, it must be remembered that this quotient merely indicates that all the glucose arising in the katabolism of a given amount of protein fails of utiliza-

[15] Arch. Int. Med., 1915, xvi, 693.

tion and is excreted. Persistence of a high G : N ratio does not, however, necessarily indicate even a maximal breakdown of body tissue. Thus two cases may each show equally high G : N ratios, but the one individual may excrete much less glucose and nitrogen than the other. In this case the prognosis would obviously be more favorable, other factors being equal. The duration of the disease, the degree of hyperglycemia, effect of ingestion of carbohydrates on the blood sugar and the glycosuria, the severity of other clinical symptoms, and the nature of previous treatment must also be carefully considered in judging of the prognostic value of this ratio in any particular instance. This is well exemplified by the very interesting case of Geyelin and Du Bois, in which a suddenly developing complete diabetes with high G : N ratio rapidly subsided under judicious treatment. This patient also illustrates the important fact that a high G : N ratio is not without exception an indication of a fatal termination of the disease.

In several instances recently studied the G : N ratio has slightly exceeded the value 3.4 : 1. In such subjects it is probable that carbohydrate already present in the body plays a role. The excretion of this carbohydrate as glucose during the fasting periods is the very probable cause of the G : N ratios of these cases being higher than 3.4 : 1, which has been shown by our work to represent in complete diabetes the average value of this quotient for urine. It is very probable that had the fasting days in these cases having G : N ratios over 3.4 : 1 been sufficiently numerous this lower ratio would have been observed.

SUMMARY. By means of improved experimental methods it could be established that the fasting urinary G : N ratio of severe diabetes mellitus is about 3.4 : 1. The G : N ratio is, therefore, to be regarded as a definite index of the severity of this disease. In association with other factors to be considered, the G : N ratio is a valuable prognostic sign.

OBSERVATIONS ON THE STARVATION TREATMENT OF DIABETES.

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AND

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FOR the past year we have been treating all cases of diabetes admitted to the Royal Victoria Hospital, on the starvation plan.

Those patients who remained under the strict supervision, and

those who, when away, made an intelligent effort to carry out the treatment, did well, and have remained sugar-free on the prescribed diet, proved after varying periods to be suited to their tolerance.

Difficulties, however, arose with those unwilling, or unable, to follow the directions, and these difficulties, needless to say, were numerous. No doubt the supreme difficulty will always be that either the patient, or the doctor, fails to appreciate the need of strict attention to the treatment. So much precision in the diet is necessary, for severe cases, that even in the hospital routine, it has often been extremely difficult to carry out a successful treatment except with full coöperation of the patient.

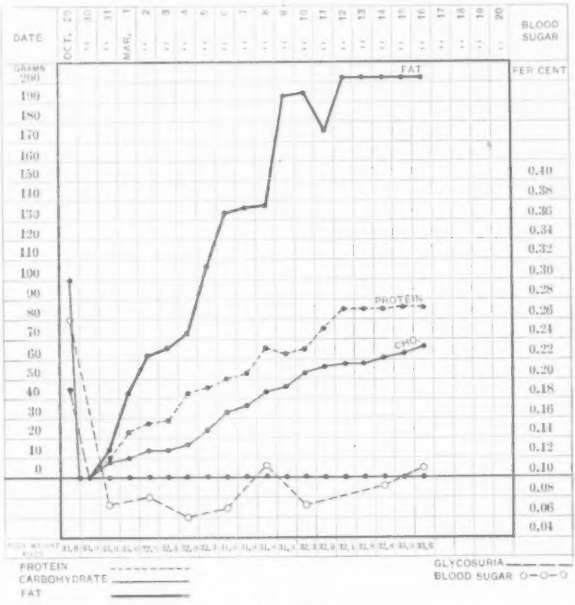

CHART I.

Again, our knowledge of the exact values of foodstuffs is still insufficient, more especially that branch relating to appreciation of the values of cooked and uncooked foods, notably the carbohydrates, and the proteins with their CHO content.

That there is greater need of standardization in our dietetic treatment is more and more apparent, and without an attempt to make clear the values of foods given, it is difficult for observers to fully coöperate in work of this nature.

The simple example may be cited of CHO values in various vegetables; while some observers compute in their estimate of CHO

food administered only the available CHO, others again include the total amount, of which unused cellulose forms a considerable portion, and alters entirely the value of our given foods. So, too, in boiled vegetables, while some compute the water in which CHO are boiled, others discard it, even though a not inconsiderable amount of available food in it should be estimated if we are to aim at exactness in our computations.

On the other hand, it is a matter of occasional surprise that patients can sometimes disregard these dietetic prescriptions with impunity. Particularly noteworthy is an instance of a patient with moderately severe diabetes, upon whom, after successful starvation treatment had conferred benefit, periodical alcoholic bouts and late nights of dissipation seemed to have no deleterious effects.

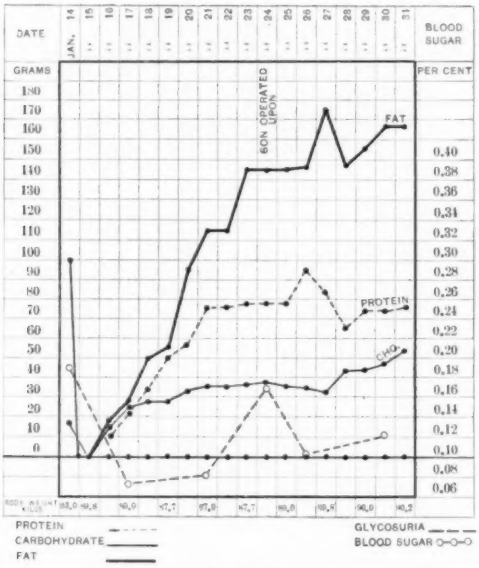

CHART II.

In two of our cases, however, fatigue and nervousness seemed to markedly aggravate an already existing glycosuria, this view coinciding with those recently emphasized by Cannon (see Chart II).

In one much-worried patient, with a glycosuria of 12 per cent., rest and relief from anxiety alone were followed by a reduction to 2 per cent. on the following day.

As a rule, one or two days of starvation sufficed to render the urine sugar-free, and in only one instance was the period as long as five days.

In the moderately severe cases it was found that patients could be raised to a tolerance of high caloric value in amazingly short time (See Chart I), but it has not seemed possible in raising the CHO tolerance to avoid the return of a hyperglycemia. In fact, in our limited experience it would seem that the metabolic disturbance which is implied by the term diabetes is not eradicated by any dietetic treatment, but merely subdued during the period of absolute precise treatment.

During the starvation treatment it was not found necessary, except in one instance, to use alcohol during the early days of treatment. In one case (Chart I), all forms of foodstuffs were raised to a very high level of value and maintained with excellent results while the patient was under supervision; but, as a rule, it was found that the more gradual and slow attaining of tolerance seemed the wiser plan, and when accompanied by a weekly starvation day the level of tolerance was raised with much greater success.

In the satisfactory cases the striking features were the speed at which sufficient satisfying food could be given, and the patient maintained upon a low level of food supply with an absence of hunger, thirst, fatigue, or loss of weight, and a general feeling of well-being seemed to exist when the proper level was maintained.

During the early treatment the loss of weight seemed rarely to be marked—in one case over 20 pounds, and in two others 13 pounds—while in the rest the loss of weight never exceeded 5 pounds. Later on the normal weight was either recovered or remained but little below the original level. Perhaps insufficient attention has been drawn to this fact, and the impression is too wide-spread that the starvation treatment is one of reduction, with severe emaciation, whereas in reality the subjective and objective evidences of starvation are not present.

Examination of Blood-sugar. The blood-sugar was periodically examined in every case. After the patient's admission an estimate was first formed of the approximate severity of the disease, together with the percentage of blood-sugar and then 100 grams of glucose were given on the first day of starvation, and the blood-sugar thereafter determined every hour for four hours.

Experience in the case of three or four patients, however, revealed the fact that four hours was an insufficient period in which properly to estimate the blood-sugar curves. We have recently extended these observations to cover twelve to twenty-four hours, and discovered thereupon that the hyperglycemia is more persistent than had been supposed.

The results by comparison with normal individuals were of great interest:

Experimental Glucose Curve of Normal Individuals. In the normal person there is, of course, an increase of blood-sugar after 100 grams of glucose have been administered, but the curve

occupies a much lower level, usually dropping below the normal in two or three hours. The maximum is attained at the end of the first hour, becomes normal again at the second hour, goes below the normal at the end of the third hour, and finally rises again to normal in four to five hours (see Chart III).

The normal threshold we regard as 0.14 per cent.

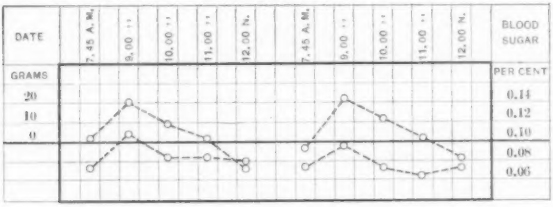

CHART III.

EXPERIMENTAL GLUCOSE CURVE OF DIABETICS. In diabetes, however, the curve was markedly altered and prolonged, as was found in repeated observations, in which, of course, we kept all individuals under exactly uniform conditions.

One hour after administration of the glucose the percentage rose, attaining its maximum at the end of the second hour, rarely at the end of the third.

The decline followed, but at a rate much slower than in normal individuals. The implication is that in diabetes, the liver not being able to hold the sugar in amount and duration as in the normal, causes a higher percentage of blood-sugar to appear.

The excursion is greater, the ascent more acute, the maximum appearing sometimes rapidly, sometimes more slowly, the variations, however, not depending on severity. As a rule, the maximum was reached at the end of two hours, and the decline was slow, occupying often eight to twelve hours (see Chart IV).

These observations seem to confirm those of Falta, who emphasized their importance in diabetes.

The abnormally slow decline in the blood-sugar curve in the later hours of the test on diabetics, possibly suggests some kind of kidney-block, and varies according to the rate of excretion, and in part, too, of course, to the degree of combustion.

RENAL BLOCK. This question of kidney-block is apparently an unsolved problem, but the more careful and repeated examinations for blood-sugar have demonstrated its importance as well as the intimate relation in many cases between glycosuria and renal function. It was found that with starvation the disappearance of the glycosuria has usually preceded the subsidence of hyperglycemia. However, our experience in one respect is at variance with Joslin,

who states that during starvation the hyperglycemia persisted, while in the majority of our cases it disappeared rapidly with starvation.[1]

With gradual increase in the diet, however, the blood-sugar rose to an abnormal degree, usually in the absence of glycosuria.

Various factors seem to play a part in inducing block, and the causes are difficult to explain; in three of our cases the values ran as high as 0.22 per cent. 0.26 per cent. and 0.28 per cent. without glycosuria. In other cases with glycosuria of long duration the block appeared, though at a lower level.

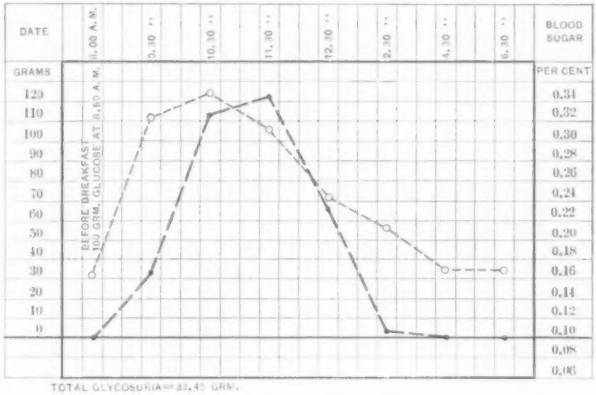

CHART IV.

A certain prognostic importance is attached to renal block in diabetes, for it would seem that the degree of hyperglycemia varies directly with the tendency to progression and the development of complications.

An insidious and progressive diabetes may often be overlooked when glycosuria is absent, and when an appreciation of the block may yield a more intelligent means of dealing with the patient.

Evidently sufficient stress is not laid upon the hour at which these estimates are made. Thus, for example, the hyperglycemia came on at first about two hours after meals, at which time we think the estimates should always be made as giving us the best guide to the diabetic changes. Blood-sugars in the majority of our diabetics were found to be normal in the early morning before breakfast, while two hours after meals a hyperglycemia was evident, this depending, of course, in part upon the diet. Often, however, when the diet was restricted in accordance with the treatment the same experience occurred.

[1] Arch. Int. Med., vol. xvi, p. 703.

The following figures will indicate the differences: Before breakfast: 0.11 per cent., 0.10 per cent., 0.18 per cent. After breakfast: 0.15 per cent., 0.16 per cent., 0.24 per cent.

Renal Glycosuria and Block. In one of our patients, persistent glycosuria appeared whenever the blood-sugar rose to a level of 0.11 per cent.; at no time was there much glycosuria, and he always reacted to starvation; 27 grams of carbohydrate per day would induce a glycosuria which was not increased with an intake up to 50 grams.

Before meals his blood-sugar was 0.08 to 0.09 per cent., while after a mixed meal his blood-sugar rose to 0.11, or 0.12 per cent. with slightly glycosuria (see Chart V).

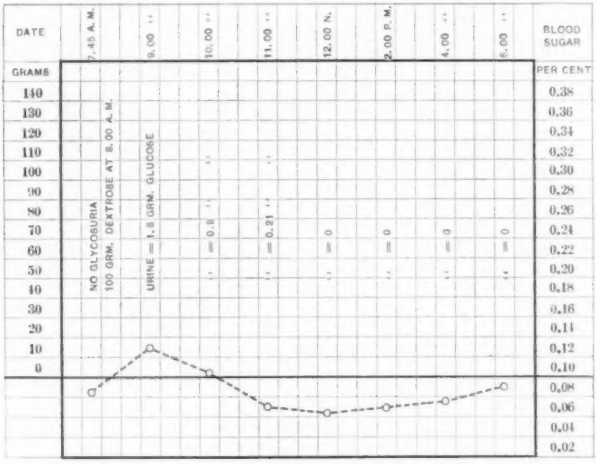

Chart V.

As a result of recent work, no doubt, the more frequent estimations of blood-sugar will demonstrate that renal diabetes so-called is less rare than has hitherto been believed.

Test Diet. In some cases a patient's tolerance seems to alter in a very short time, and appreciation of this is of the greatest importance in the use of test diets. Thus, for example, in one individual who had had a fat protein diet for three days, preceded by a low CHO intake for one week, there was a D : N ratio of 2.77 per cent., showing an inability to burn 43 per cent. of protein carbohydrates. He continued on a fat protein diet for twenty-one days, and during the first fourteen days the D : N ratio varied markedly, finally dropping to zero on the sixteenth day. On this day he burned 36 grams of protein CHO as well as 2 grams of CHO in 100 grams of chicken (*i. e.*, 38 grams CHO).

Reading the variations according to the Lusk-Falta formula we found the following:

$$\frac{35.9 \times 100}{12.97 \times 3.65 + 0} = 75.6 \qquad \text{13 days later,} \quad \frac{3.08 \times 100}{9.32 \times 3.65 + 2} = 8.5$$

Acidosis. Two important points are worthy of note in our observations:

1. The ferric chloride reaction is sometimes absent when acidosis is present, and is less sensitive, too, than the nitro-prusside reaction.
2. The urine does not always show a reaction for acidosis even when the blood gives a positive quantitative result. This latter is important as reminding us that the excretion of the acid bodies is not necessarily an index of the degree of acidosis.

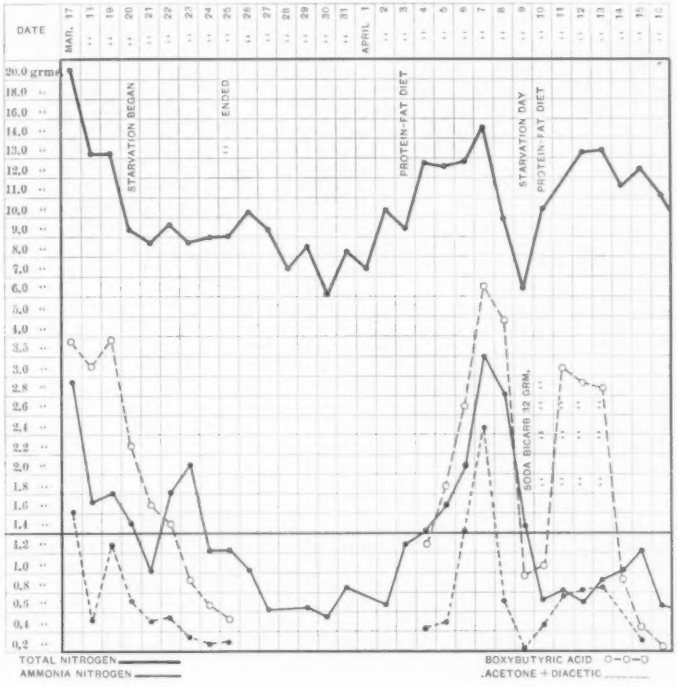

Chart VI.

Starvation in the ordinary individual usually results in acidosis, while in diabetes the reverse occurs. Allen, indeed, lays stress on this feature, and insists on the need of eliminating ketone bodies from the blood by means of starvation.

Sometimes, however, in our cases, acidosis was initiated by the starvation, at other times a preëxisting acidosis was increased, though usually it disappeared. Evidently there is a variation due to many circumstances, though starvation ultimately does make the urine acid-free.

In one persistent case of very mild diabetes, with prolonged mild acidosis, interrupted periods of a fat-free diet seemed especially useful in clearing up remnants of the acidosis.

In one very severe case in which the acidosis disappeared on starvation, it developed again on a protein fat diet, and later on disappeared with one day of starvation. Sodium bicarbonate was given (32 grams per diem) for five days, with resulting elimination of more ketone bodies. Excretion of these bodies ceased again with cessation of bicarbonate administration (see Chart VI).

Another experience worthy of note is the varying ratio of the acetone bodies to β-oxybutyric acid. Sometimes there is much acetone and little β-oxybutyric acid, and sometimes the reverse occurs. There seems to be little constancy, and the percentage of 60 to 80, as usually recorded is subject to many wide exceptions.

THE INFLUENCE OF ACIDOSIS ON HYPERGLYCEMIA IN DIABETES MELLITUS.

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new york city.

(From the Laboratory of Physiological Chemistry of the Pathological Department of Mount Sinai Hospital, New York City.)

Total fasting or the prolonged withdrawal of carbohydrates from the dietary of a normal or diabetic individual leads to the production of an acidosis. This is usually explained on the following grounds: (1) fats are oxidized secondarily through the combustion of carbohydrates:[2] (2) because of the withdrawal of carbohydrates (and also with the limitation of proteins) more fat than usual is called upon to supply the body energy. The resulting increased mobilization of fats associated with their incomplete combustion leads to the production of acid bodies. An increased protein metabolism (occurring synchronously) may add to or augment the production of similar substances.

[1] Work done under the tenure of the Moses Heineman Fellowship in Pathology.
[2] Naunyn: Der Diabetes Mellitus, 1906, p. 221.

The general effect of the overproduction of such bodies upon the organism is the coupling-up of all available alkalies. This in turn leads to a reduction of the amount of fixed alkali and ammonia in the body, a condition which constitutes an acidosis.

The acidosis may manifest itself in the following ways: (1) increased acidity of the urine, so that very large amounts of alkali are required to render it alkaline; (2) increased hydrogen-ion concentration of the blood serum; (3) diminished combining power of the serum for carbon dioxide, and hence (4) reduced carbon dioxide tension in the alveolar air; (5) increased ammonia output in the urine, combined with elimination of ketone bodies.

In addition to the other effects of acidosis on the body it has been shown by a number of investigators that it is in itself capable of inducing a glycosuria (so-called "Säure-Diabetes"). Elias[3] has demonstrated that the production of an artificial acidosis leads to a marked mobilization of glycogen from the liver and other depots. So too Pavy,[4] Kulz,[5] and Goltz[6] have shown experimentally that the intravenous and intrastomachal administration of various acids leads to a glycosuria. Numerous clinical observations of cases of acid poisoning have confirmed these findings. Moreover, Ruschhaupt[7] found that even the administration of acetone can cause a glycosuria. On the other hand, Murlin and Kramer[8] have shown that after the removal of the pancreas the introduction of sodium carbonate into the blood stream causes a diminution in the excretion of sugar. Even the respiratory quotient is increased in depancreatized animals after the administration of alkali.[9] In a recent communication, Underhill[10] shows that the control of acidosis (by means of alkali) is followed by the reduction of the glycosuria in a diabetic.

The intermediate step between a glycogen mobilization (due to acidosis) and glycosuria is an increase in the blood sugar. Another factor which may influence the degree of hyperglycemia is the function of the kidneys. Epstein and Baehr[11] have shown that in depancreatized animals, with impaired or abolished kidney function, the liberated sugar accumulates in the blood, causing very marked hyperglycemia. The impairment of renal function in these experiments is attributed to the acidosis. The effect of acidosis upon the blood-sugar may thus be twofold: (1) through its effect on the liver and muscles, causing a mobilization of glycogen, and (2) by interference with renal elimination of sugar, leading to its accumulation in the blood.

[3] Biochem. Ztschr., 1913, vii, 331.
[4] Naunyn, loc cit., p. 40.
[5] Pflüger's Arch., 1881, xxiv, 97.
[6] Centralbl. f. d. med. Wissensch., 1867, v, 705.
[7] Arch. f. exp. Path. u. Pharm., 1900, xliv, 126.
[8] Jour. Biol. Chem., 1913, xv, 365.
[9] Cited from F. P. Underhill: Tr. Soc. Exp. Biol. and Med., 1916, xiii, 111.
[10] Tr. Soc. Exp. Biol. and Med., 1916, xiii, 111.
[11] Jour. Biol. Chem., 1916, xxiv, 1.

The introduction of prolonged fasting as a means of treating diabetes has revealed the fact that not only does the glycosuria frequently disappear, but also that the acidosis clears up as well. However, observation of a large series of cases under such treatment has shown that whereas certain cases lose their glycosuria, hyperglycemia, and acidosis, certain others develop an acidosis or exhibit a very marked increase thereof. If not immediately controlled such cases prove to be rapidly fatal. On this basis, cases of diabetes may be divided into two groups: those in which fasting controls the hyperglycemia and causes the disappearance of symptoms, and those in which the withdrawal of food (particularly of carbohydrates) causes or aggravates the acidosis, thus rendering the diabetic condition much worse.

The studies which we have made show the effect of acidosis on carbohydrate metabolism, especially in cases that are unfavorable for starvation treatment, in which a vicious cycle is established by the withdrawal of food, and more particularly of carbohydrates. It has been frequently shown (Minkowski, Magnus Levy, Joslin and others) that even in very "severe" diabetes the body has the power to oxidize carbohydrates, and that carbohydrates are specific in reducing acidosis even when the ability of the body to burn them is very low. This beneficial influence of carbohydrates on the acidosis, and subsequently on hyperglycemia and glycosuria, is demonstrated in our studies.

The following cases are supplied as examples to illustrate the above observations:

CASE I.—*Coma diabeticum, unusual hyperglycemia, associated with acidosis, in the terminal stage of the disease.*

W. S.; tailor; Austrian, aged fifty-seven years. Admitted March 22, 1916; died March 25, 1916. Chief complaints: polyuria and polydipsia for three weeks and repeated vomiting for four days. Physical examination revealed a tendency to stupor, deep inspirations, and acetone odor to the breath. On March 22 the patient was placed upon milk, 1500 c.c. per day, 5 per cent. vegetables ad. lib., Murphy infusion of 3 per cent. sodium bicarbonate (1000 c.c.) b. i. d., sodium bicarbonate by mouth, one dram, q. 2 h. The patient started to vomit and continued to expel all food and medication. Drowsiness and heavy snoring respiration became prominent. Three intravenous injections of alkali were given, but drowsiness soon merged into deep coma, and on the fourth day death intervened. All urinary examinations showed sugar, marked acetone, and diacetic acid (see Chart I).

COMMENT. Note the antemortem rise in blood-sugar (as shown in the diagram) to the unusual figure of 1 per cent. and concomitant fall in alveolar carbon dioxide. The urine was very small in amount during the entire period of observation. Some urine was lost because of involuntary micturition.

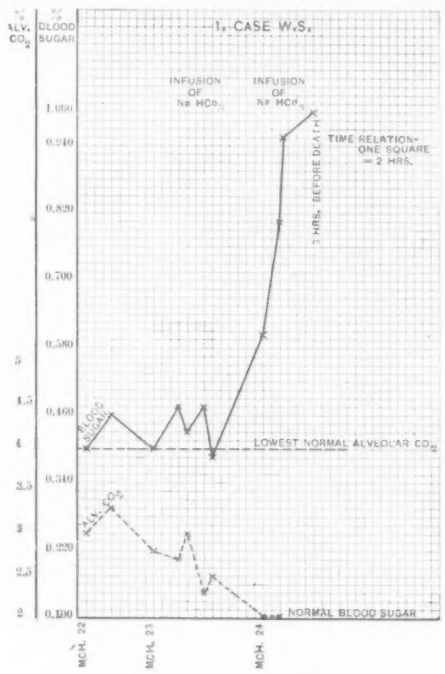

CHART I.—Case W. S.

CASE II.—*Coma diabeticum and abscess on the back.*

B. F.; aged forty-nine years. Admitted March 10, 1916; died March 17, 1916. Chief complaint: abscess on back, of two weeks' duration, and steadily increasing in size. The patient has had diabetes for nine years. Physical examination and subsequent operative procedure (on the day of admission) revealed an irregular red elevated fluctuating area in the interscapular region, discharging pus through a small sinus. Upon incision there was found an extensive cellulitis of the back, involving all of the deep tissues, and studded with necrotic material and abscess cavities. The patient was placed upon sodium bicarbonate, 1 dram every three hours, Murphy infusion of 3 per cent. sodium bicarbonate (1000 c.c.) b. i. d., whisky ½ ounce, q. 2 h., 1500 c.c. of milk per day, and infusion of digitalis, ½ ounce, t. i. d. The wound continued to drain profusely and the patient voided large amounts of urine (the average daily output being 3500 c.c.). On March 12 whisky was stopped and the carbohydrate was gradually increased in the form of 5 per cent. vegetables, until the patient, on March 15, was receiving 500 grams of 5 per cent. vegetables and 1 pint of skimmed milk. On March 16,

however, the patient started to vomit, the urinary output fell to 1990 c.c., drowsiness became more and more evident, and death ensued. All urinary examinations showed sugar, marked acetone, and diacetic acid (see Chart II).

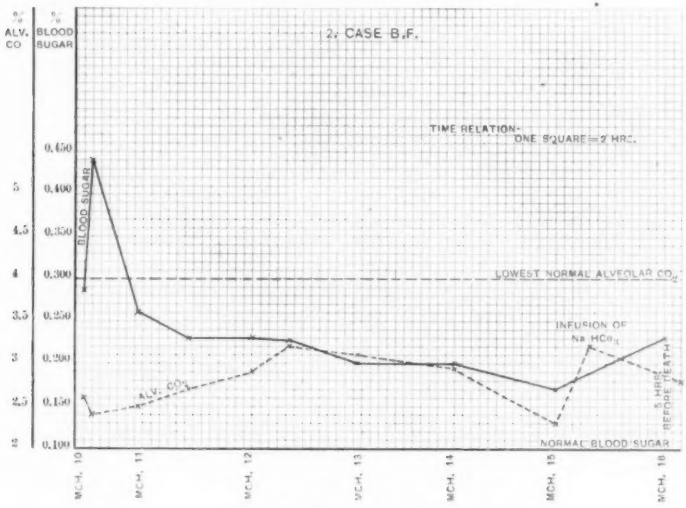

CHART II.—Case B. F.

COMMENT. This case demonstrates the effect of administration of carbohydrate and alkali on the acidosis. Associated with the reduction in the acidosis is a marked decrease in the hyperglycemia. The fall in the blood-sugar was accompanied by a reduction in the glycosuria. Just before death, however, as the urinary output diminished in amount, the alveolar carbon dioxide fell and the blood-sugar rose.

CASE III.—*Coma diabeticum following the withdrawal of food.*

E. C.; operator; aged twenty-four years. Admitted February 15, 1916; died February 25, 1916. Chief complaints: pruritus vulvæ and nocturia for three months. Physical examination revealed an acetone odor to the breath and a severe dermatitis of the thighs and vulva.

Treatment. On February 15 and 16 strict antidiabetic diet (30 grams of carbohydrate); February 17 and 18 Allen régime of whisky and water; February 19, 30 grams of 5 per cent. vegetables allowed. On the following day the patient started to vomit the whisky, then all food and medication. Murphy infusions of 3 per cent. sodium bicarbonate were then started and the diet changed to skimmed milk, 1 quart per day. Vomiting continued, and on February 23 the

patient was becoming stuporous. Carbohydrate and alkali were given liberally (by rectum, per os, and intravenously), but the patient lapsed gradually into coma and died. The urinary examination showed sugar, marked acetone, and diacetic acid (see Chart III).

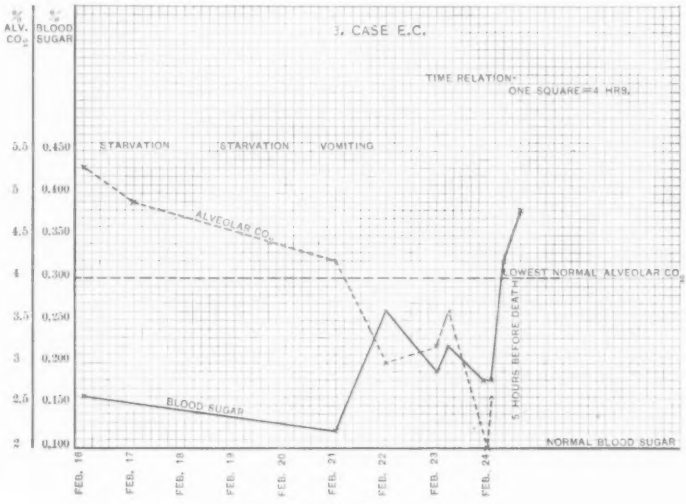

CHART III.—Case E. C.

COMMENT. The first effect of the withdrawal of food was a fall in the blood-sugar followed by a disappearance of the glycosuria. Associated with this apparently beneficial result there was a fall in the alveolar carbon dioxide and hence an increased acidosis, at first very gradual, then more rapid. As the acidosis developed the blood-sugar rose again and continued to rise.

The persistent vomiting rendered the condition uncontrollable.

CASE IV.— *Diabetic acidosis and hyperglycemia, induced by restricted diet, relieved by the liberal administration of carbohydrate.*

G. M.: housewife; Russian; aged twenty-four years, pregnant six weeks. Admitted January 21, 1916; discharged February 24, 1916. Chief complaints: polydypsia, polyuria, loss in weight for nine months. Has been on a diet all this time, and has had several fasting days. Normal weight, 146 pounds; present weight, 110 pounds. Physical examination revealed an acetone odor to the breath, emaciation, and dry skin. On January 21 the diet consisted of skimmed milk, 1 quart per day, 500 grams of 5 per cent. vegetables, whisky 2 ounces, black coffee, and chicken broth. This diet contained approximately 70 grams of carbohydrate. Upon subse-

quent days the carbohydrate allowance (mainly in the form of 5 per cent. vegetables and skimmed milk) was from January 22 to January 24, 30 grams of carbohydrate; January 24 to February 18, 32 grams; February 19 to February 22, starvation (see Chart IV).

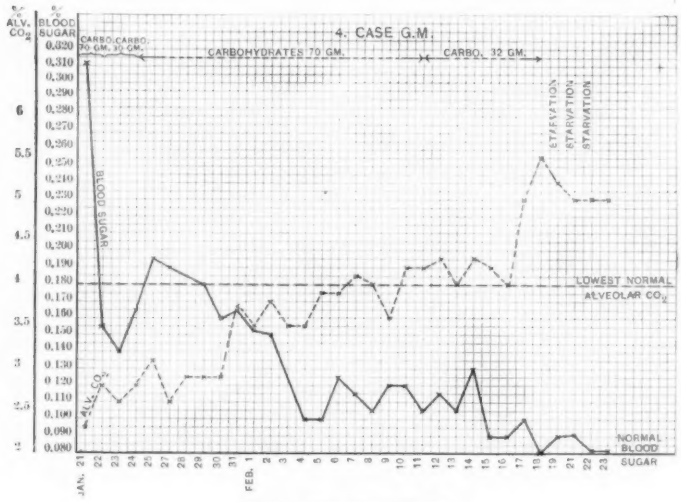
4. CASE G.M.
ALV. CO2
BLOOD SUGAR
CARBO. CARBO. 70 GM. 30 GM.
CARBOHYDRATES 70 GM.
CARBO. 32 GM.
STARVATION
STARVATION
STARVATION
BLOOD SUGAR
LOWEST NORMAL ALVEOLAR CO2
ALV. CO2
NORMAL BLOOD SUGAR
JAN. 21 22 23 24 25 27 28 29 30 31 FEB. 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 21 22 23

CHART IV.—Case G. M.

COMMENT. It is evident that this case was benefited by the liberal allowance of carbohydrate, the blood-sugar on the first day falling from 0.312 per cent. to 0.140 per cent., although the patient was receiving 70 grams of carbohydrates daily. The blood-sugar continued to fall gradually, while the alveolar carbon dioxide progressively rose. The urine was large in amount, and while on admission it showed the presence of sugar, much acetone, and diacetic acid it gradually cleared up. On February 6 the diacetic acid had disappeared, and on February 17, there was only a trace of acetone. The urine became sugar free on February 18, when the blood-sugar also fell to normal.

SUMMARY. The observations made in this study point to the following conclusions:

1. The withdrawal of food from certain cases of diabetes provokes, or aggravates the acidosis.

2. The acidosis causes an increase in the blood sugar content, in one of two ways: (*a*) by augmenting the mobilization of sugar (Case IV), and (*b*) by affecting the sugar-secreting function of the kidneys (Case I).

3. Liberal, but judicious, administration of carbohydrate may control the acidosis provoked by the withdrawal of carbohydrates

or complete fasting, thus leading to a general amelioration of the diabetes (Case IV).

4. A progressive rise in the blood-sugar content, associated with a gradual fall in the alveolar carbon dioxide is indicative of impending coma (Cases I and III).

We wish to acknowledge our indebtedness to the attending physicians of the hospital for the privilege of observing some of their cases.

A FATAL CASE OF DIABETES MELLITUS ASSOCIATED WITH LARGE-CELL HYPERPLASIA.

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and
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Ithaca, N. Y.

(From the Department of Physiology, Cornell Medical College, Ithaca, N. Y.)

The following case[1] is reported chiefly because the association of diabetes mellitus with large-cell hyperplasia has rarely been recorded. Moreover, certain histological changes to be described in this paper are believed to be an expression of a disturbance of fat metabolism, recent study of which has yielded important facts bearing, (1) upon the origin of fat under certain conditions in the spleen, liver, adrenals, lymph nodes, and bone marrow, and (2) upon the treatment of diabetes. Furthermore, the large-cell hyperplasia here described bears a certain superficial resemblance to the cellular changes in the spleen in that interesting and comparatively rare condition known as primary splenomegaly Gaucher, or Gaucher's disease, which has been believed by some, on insufficient grounds, to be a disturbance of fat metabolism.

There has been a great deal of confusion in the literature on this disease since it was first announced by Gaucher[2] in 1882, and a considerable number of mistaken diagnoses have been made. The following report may help to emphasize the importance of making

[1] Under the title "The Possible Association of Diabetes Mellitus and Splenohepatomegaly Gaucher," we gave a preliminary report of this case in the Proceedings of the Society for Experimental Biology and Medicine, New York, November 17, 1915. As some others have done, we depended mainly upon the histological examination of the tissues—spleen, liver, and lymph glands—in making our decision, though we recognized that the clinical history of the case did not support us. We take this opportunity to present the facts which establish the correct diagnosis. The case presents some unique points as far as the pathology in diabetes is concerned. As far as we can learn they have not been reported before in this country.

[2] De l'epithelioma primitif de la rate, Paris, 1882.

careful histological, polariscopic, and microchemical tests when it comes to deciding whether or not the pathology of a given spleen is that of true Gaucher's disease. (See the papers by Brill and Mandlebaum[3] and Mandlebaum and Downey.[4 5]

CASE NOTES.—S. R. J., male; white; American; aged twenty-eight years; single; civil engineer. Patient complains of weakness, excessive thirst, and frequent and copious urination, insomnia, and constipation.

In the spring of 1911 patient first noticed that he had excessive thirst and frequent urination. In the summer of 1911 sugar was found in his urine.

Previous Illness. During the preceding four years he had been working out of doors at his profession, engineering, chiefly field and irrigation work. Had enjoyed unusual health. In the year 1910 patient was struck by timber on right shoulder. This caused a slight injury, which produced a lameness lasting only for a day or two. In the year 1907 patient had a diseased lymphatic gland removed from the left inguinal region. This is thought to have been caused by an infection in the foot.

As a child the patient had slight attacks of scarlet fever, measles, and mumps, from which he made good recoveries. No history of nervous or venereal disease.

Family History. Father living at sixty-four years of age; well. Mother living at sixty-two years of age; well. Patient has two brothers, living and well. No history of diabetes among the immediate or collateral relatives.

Weight. Best weight, 145 pounds, 1909. Spring, 1912, 136 pounds. July 5, 1912, 134 pounds.

Physical Examination, July 5, 1912. Medium height. Fairly well developed. Thin panniculus. Teeth: many filled. Marked pyorrhea of molars. Tongue swollen and teeth-marked. Lungs clear; no areas of dulness; no rales. Heart normal in size and position. No bruit. Reduplication of second sound at apex on the tenth to twentieth beat. Rate in upright position, 108 per minute; horizontal, 80 per minute. Systolic blood-pressure, 110 mm. Nothing abnormal noted in the abdomen.

BLOOD EXAMINATIONS.

July 6, 1912. Total leukocytes, 6,040. Red cells, 5,420,000. Differential leukocyte count:

Large lymphocytes	4.0 per cent.
Small lymphocytes	19.0 "
Transitionals	3.0 "
Polynuclear neutrophiles	72.0 "
Polynuclear basophiles	1.0 "

[3] Folia Hematologica, 1916.
[4] JOUR. AM. MED. SC., 1913, cxlvi, 863.
[5] Johns Hopkins Hosp. Bull., 1916, xxvii, 302.

October 9, 1912. Differential count:

Large lymphocytes	7.1 per cent.
Small lymphocytes	9.8 "
Transitionals	5.3 "
Polynuclear neutrophiles	73.6 "
Polynuclear eosinophiles	1.3 "
Polynuclear basophiles	0.9 "
Large broken-down white cells	1.7 "

July 17, 1913. Differential count:

Large lymphocytes	13.4 per cent.
Small lymphocytes	1.8 "
Transitionals	1.2 "
Polynuclear neutrophiles	78.0 "
Polynuclear eosinophiles	3.6 "
Normoblasts	14.0 "

Early in the illness (September, 1912) the patient was examined in consultation by Dr. Elliot P. Joslin, who also noted nothing abnormal in the patient's abdomen. Our attention was not directed to the spleen, however, and it is not improbable that a slight enlargement of it was overlooked.

Because of the prominence of the patient and of his family, many physicians in various parts of the United States were consulted in this case. Practically every known dietary and medical treatment was employed at the suggestion of these various clinicians. The patient resided in Ithaca; the general clinical supervision of the case and the urine examinations were conducted by one of us in Rochester.

In the year 1912, when this patient was under observation, clinicians generally believed that the most important factor in the problem of diabetes was carbohydrate metabolism. The significance of fat and protein metabolism and the total caloric needs of the diabetic were not clearly understood, and were given only minor consideration. It was generally believed that a patient with diabetes must, for the maintenance of life and comparative health, have a minimum food intake of at least 30 calories per kilo of body weight. On this basis the patient, weighing approximately 134 pounds or 61 kilos, would have required daily at least 1830 calories while at rest and at least 15 per cent. more, or approximately 2200 calories, while undergoing moderate exercise.

The clinical experience of one of us (Williams) during the past year, in which more than 50 cases have been accurately studied with reference to this point as result of the epoch-making work of Allen in the Rockefeller Institute, demonstrates that patients can live in comparatively good health on total food intakes far below these minimum standards which had hitherto been thought necessary.

Furthermore, recent clinical experience has shown that the feeding of the average diabetic beyond this formerly supposed normal minimum requirement of 30 calories per kilo of body weight will

TABLE I.—SHOWING URINE EXAMINATION AND FOOD INTAKE ON VARIOUS DAYS THROUGHOUT TREATMENT.

Date.	Urine.					Diet.				
	Volume.	Specific gravity.	Diacetic acid.	Total NH_3 (Folin).	Sugar (polar).	Carbohydrate.	Protein.	Fat.	Alcohol.	Calories.
1912										
July 5	1200	1023	++	1.9	48	20	100	200	0	2310
6	960	1026	++	2.1	27	65	100	200	0	2500
27	2490	1023	+	0.6	30	90	33	74	0	905
Aug. 8	2660	1030	++	2.7	86	190	75	200	0	3000+
Oct. 20	2040	1031	+	0.6	45	64	75	30	12	1010
31	2460	1026	0	0.3	38	45	75	30	12	949
Nov. 12	2160	1025	0	0.5	56	56	75	30	12	878
1913										
Jan. 28	4080	1031	+++	2.6	122	35	100	200	0	2370
Feb. 2	3630	1033	+++	3.0	152	66	90	200	0	2450
June 12	3600	1030	++++	4.1	108	90	100	200	0	2640
July 27	3630	1030	++++	4.4	123	200	150	180+	0	3000
31	3930	1027	++++	3.3	172	200	150	180+	0	3000

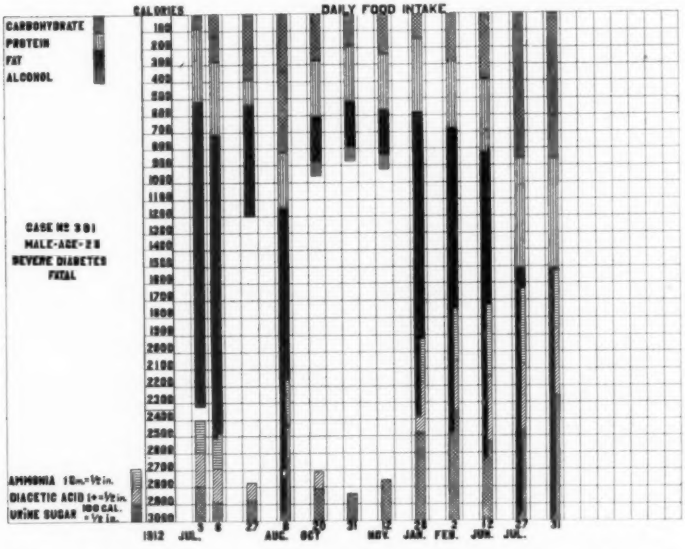

CHART I. Plotted from Table I.—Showing graphically the relation between the food intake and urine outgo. Food intake for each day reads from above down in calories. The urine examinations read from the bottom up as shown by key at end of chart. It will be noted that on days when much food was fed, particularly fat, the acidosis as measured by the ammonia and diacetic acid excretion was worse. On August 8 the patient was given an oatmeal diet. The various diets shown in this chart represent the culminations of various dietary procedures.

precipitate in the majority of cases of advanced diabetes both glycosuria and acidosis; and if, as was formerly taught, the patient be fed much in excess of this so-called standard, not only will his tolerance for carbohydrate be seriously impaired but his acidosis will be proportionately increased. This fact is illustrated by Table I and Chart I.

In a study of this table it will be observed that on those days when the patient was fed a diet low in fat the severity of his acidosis, as measured by the ammonia output, declined. It is altogether probable that had this dietary procedure been pursued further the diabetic condition would have been ameliorated, for when it was thought desirable to restore the losing weight of the patient and apparent weakness by feeding the patient large amounts of fat his acidosis increased in severity. This is the justification for the belief, from a clinical stand-point, that the patient had a serious failure in fat metabolism.

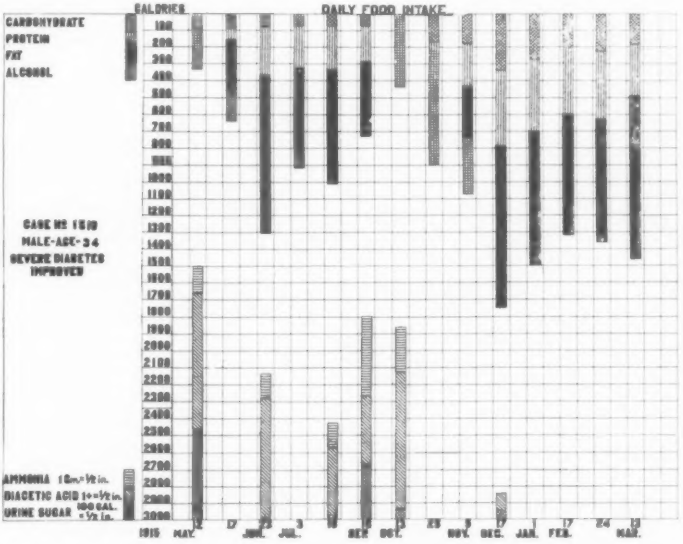

CHART II.—Illustrates present method of treating diabetes. Compare with Chart I. Severe diabetes and lipoidemia in a young male. Case similar in many respects to the one described in this paper. This patient had a marked acidosis and very low tolerance for food. There was almost complete intolerance for fat. By feeding the patient on fat-free and low-fat diets his condition has been much improved, although the cholesterol content of the blood remains high. The data above shown are from test days after periods of such treatment. Food intake reads from above down in calories, the different food principles being represented by the different cross-hatchings as shown in the key. The urine outgo reads from the bottom up; urine sugar plotted in calories; diacetic acid and ammonia are shown in the key.

Because of this erroneous belief about the normal minimum food requirement, and because of the then current clinical teaching, in effect that fat should constitute the major portion of a diabetic's diet, this patient was fed fat in considerable amounts, as indicated in Table I and Chart I.

To contrast the effects of high and low fat content in the diet in severe diabetes we insert a graphic record (Chart II) of a case now under treatment. Table II gives dietetic and other details. It will be observed that the cholesterol content of this patient's blood has been very high. The presence of this substance in the tissues and certain of its experimental effects will be discussed later.

TABLE II.

Blood removed.	Diet previous twenty-four hours.				Urine sugar.	Free ammonia.	CO_2 in lung air, mm.	Cholesterol per 100 c.c. blood, mg.
	Carbohydrate.	Protein.	Fat.	Calories.				
1916								
Mar. 14	44	69	108	1428	0	0	36.2	510[6]
April 10	43	71	88	1258	40	0.82	41.2	428
May 11	33	84	96	1363	..	..	30.0	833
15	61	35	21	674	101	2.81	31.4	717
23	No food 15 hours previous				19	1.21	39.3	833

Returning to the case under discussion, we may say that there was nothing unusual in the general course of the disease. It progressed steadily and the patient died in coma August 1, 1913.

Postmortem Examination. Body was embalmed one hour after death. The fluid used contained about 7 per cent. of formalin and a small amount of carbolic acid. Postmortem was held twelve hours after death, the object at the time being mainly to secure the pancreas. Abdominal organs only were examined.

Macroscopic findings: All organs had a normal appearance except the spleen, which was somewhat enlarged. It weighed 330 gms. Shape not unusual; dimensions: 13 x 10.5 x 6 cm. Color normal, both superficially and when sectioned. No amyloid areas.

Microscopic examination:[7] Pancreas, liver, spleen, kidneys, adrenals, and lymph glands were sectioned. Specimens were fixed in formalin, Zenker's fluid, and osmic acid.

Kidneys normal.

Pancreas: No generalized increase in connective tissue, but some

[6] Cholesterol estimation was made by Prof. W. R. Bloor, whose method (Jour. Biol. Chem., 1916, xxiv, 227) is employed in the tests. Normal blood contains between 170 and 240 mg. cholesterol per 100 c.c.

[7] Specimens of the spleen and pancreas were examined by Drs. L. Hektoen, James T. Ewing, E. L. Opie, and A. S. Warthin, to whom we desire to express our thanks for valuable reports and suggestions.

indication of atrophy, with duct stasis. Few areas of strongly acidophile alveoli. Islets normal in number and distribution. Some islets enlarged, in few instances to twice ordinary size. No marked abnormality of structure shown, but there was a tendency to hypertrophy and to contain hyperchromatic nuclei. Islet cells closely packed together, and difficult to distinguish, with cell masses separated by conspicuous capillaries, walls of which appeared somewhat thickened. Slight sclerosis. No evidence of hyaline change in islet epithelium (see Fig. 1).

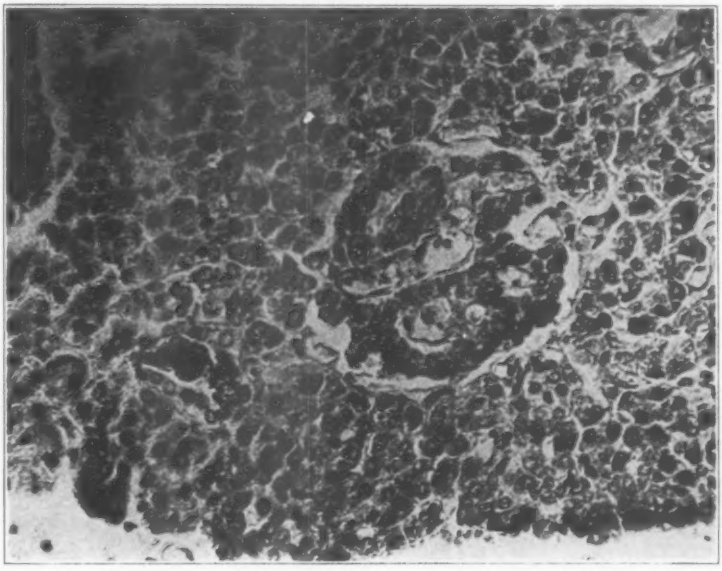

FIG. 1.—Section of the pancreas, showing a single islet. Zenker fixation. Iron hematoxylin. × 400.

Spleen: The spleen throughout contained numerous large cells. These cells were mostly round or oval, and were of varied size. They were especially abundant in the pulp, but some could be seen to penetrate into the periphery of the nodules. Nodules otherwise were normal. Scarcely any sclerosis. No giant cells noted. Further description given below (see Fig. 2).

Lymph glands: Two lymph glands from the duodenal mesentery were sectioned. They showed the same large cells as did the spleen, though the cells were smaller and not so plentiful as in the spleen. No pigment was present (see Fig. 3).

Liver: A few cells bearing superficial resemblance to those in the spleen were found in the liver sinusoids; not more than three or

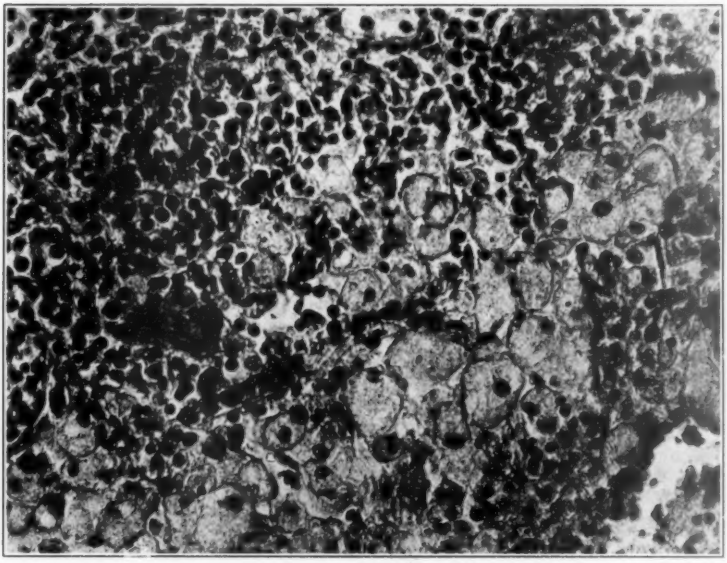

FIG. 2.—Section of the spleen, showing large-cell hyperplasia. Zenker. Hematoxylin and eosin. × ca. 350.

FIG. 3.—Section of a mesenteric lymph gland. A few large hyperplasia cells are seen about the middle of the section. Zenker. Hematoxylin and eosin. × ca. 350.

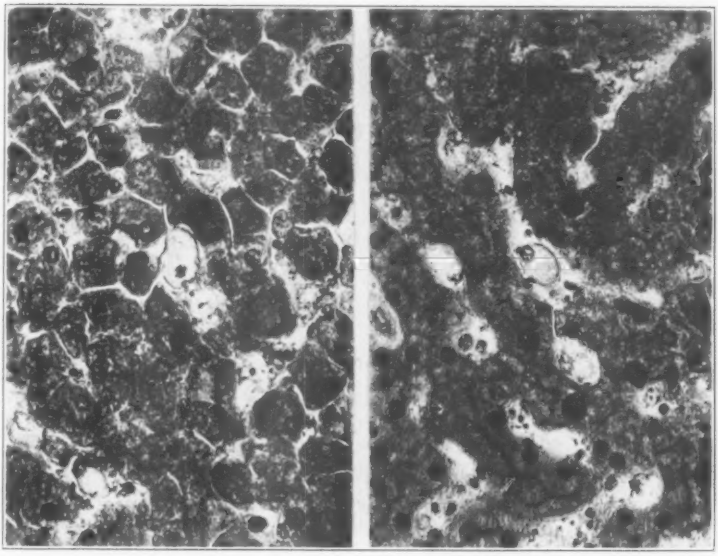

FIG. 4.—Two sections of liver. In the middle of each section may be seen a single Kupfer cell, located in a sinusoid. See text for description. Formalin. Iron-hematoxylin. × 350.

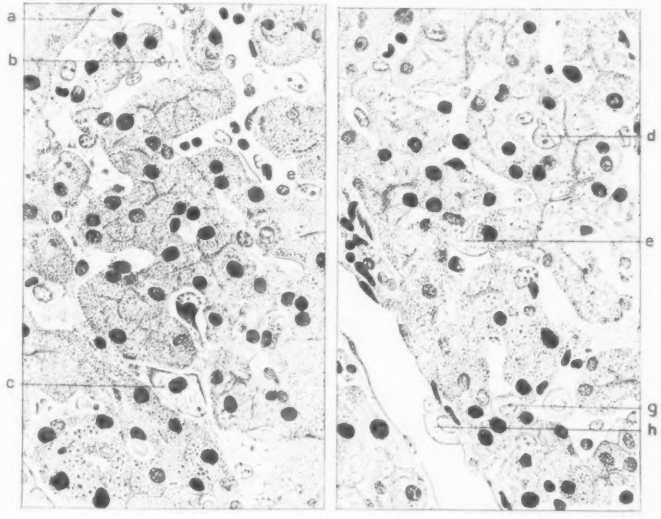

FIG. 5.—Microprojection drawing of two liver sections. Kupfer cells are seen at *a*, *b*, *c*, *d*, *e*. At *a* large cell which apparently has wandered into a vein is marked. × 400.

four generally were seen in a lobule, though occasionally they were fairly numerous (see Figs. 4 and 5).

Further details about the liver and adrenal glands are given in the following comments, which were made, in a personal communication to the authors, by Dr. Frank S. Mandlebaum,[8] who kindly examined the tissues:

"It cannot be denied that the large cells in the spleen have a certain resemblance to the large cells of Gaucher's disease, but pictures of this kind are found in a variety of pathological processes. The cells in your cases are more rounded in outline than those of Gaucher's disease, the characteristic wrinkled and streaked appearance of the cytoplasm is missing, and the impression is obtained that some substance originally contained in the cells has been dissolved out in the process of hardening and embedding. Furthermore, dilated venous sinuses filled with blood and large cells are not prominent. The sections of the liver do not in any way resemble those of Gaucher's disease, even though some large cells are present in the sinusoids. The lesion is a granular degeneration with hypertrophy of the stellate cells of Kupfer (see Figs. 4 and 5), with secondary proliferation and desquamation. Some of these cells may have been carried to the liver from the spleen through the portal circulation. The lesion in the lymph node is a marked hyperplasia of the cellular reticulum such as is frequently found in many pathological processes, but bears no resemblance whatever to the lesion of Gaucher's disease.

"Examination of the blocks of tissue of the spleen and liver reveal the true nature of the pathological process. Fortunately the tissues were fixed and preserved in formalin, therefore the substance in the large cells can be identified. Frozen sections of the spleen stained with Sudan III and Nile blue show the presence in the large cells of a considerable amount of neutral fat and lipoids. The polariscope shows anisotropic bodies which disappear on heating and reappear on cooling, thus proving the presence of cholesterin esters. Polariscopic examination of liver sections stained with Nile blue shows that the cholesterin esters are present in the stellate cells of Kupfer. Unfortunately no material from the lymph nodes is available. therefore lipoid tests cannot be made. I feel, however, that the large swollen reticular cells in the lymph nodes would show the same microchemical and polariscopic reactions.

"Although the histological picture in your case is sufficient proof that this is not an instance of Gaucher's disease, the simple presence of fat and lipoids in the large cells is positive evidence that the case does not belong to this group, for these substances have never been found in any of the authentic cases. I might also say that the clinical history of the case, as published in your preliminary

[8] This case is the one referred to by Drs. Mandlebaum and Downey in their paper in the Johns Hopkins Hosp. Bull., April, 1916, vol. xxvii, No. 302.

report, together with the autopsy findings, are not suggestive of Gaucher's disease.

"I have no hesitancy, therefore, in stating that your case is one of lipoid deposits in the spleen and other organs, due to diabetes with a probable lipoidemia."

In a later letter Dr. Mandlebaum wrote to us concerning the adrenals as follows:

"Polariscopic examination of frozen unstained sections of the adrenal shows an appreciable increase of double refracting substances, especially confined to the zona glomerulosa and zona reticulosa, with some infiltration of the zona fasciculata as well. These substances disappear on heating and reappear on cooling. When frozen sections are stained with Nile blue a confirmation of the above findings is obtained. With Sudan III the cells of the zona glomerulosa are filled with bright yellow droplets. The cells of the zona fasciculosa appear enlarged, with the yellow droplets at the periphery of the cells and in the cells in the walls of the capillaries. The cells of the zona reticulosa are more completely filled with these droplets. Several small islands of cortical cells are found in the medullary portion of the gland, giving typical reactions with Nile blue and Sudan III.

"Treating sections of the adrenal with alcohol causes a complete disappearance of the anisotropic bodies, and upon subsequent staining with Nile blue and Sudan III no reactions for lipoids are obtained.

"Paraffin sections stained with hematoxylin and with Van Gieson show hypertrophy of the cells of the zona glomerulosa. These cells are increased in number and in size, and some have undergone granular degeneration. The hypertrophy of the cells is even more marked in the zona fasciculata and corresponds to the lipoid infiltration produced experimentally in rabbits and guinea-pigs by feeding with cholesterol (Antischow). The findings in the adrenal are still further proof of the probable lipoidemia in your case."

A fact worthy of note in this case is the absence of evidence of malfunctioning islets in the pancreas. Other instances of this sort are well known. On the other hand, degenerative changes in the islets have frequently been seen in diabetes, both in the human subject and in experimental animals. The amount of islet tissue necessary doubtless varies in different animals. In unpublished experiments by one of us in Ithaca with Dr. C. W. Webb, of Clifton Springs, N. Y., we have been astonished to see several dogs live a number of weeks with an extraordinary small amount of islet tissue. One dog had the head of the pancreas removed and the distal duct tied. He lived six months, free from glycosuria as long as he was given meat only, on which diet his weight decreased from 11 kg. to 5.5 kg. He developed distemper and was killed. We could find nothing but a strand of connective tissue one inch long repre-

senting the part of the pancreas left in the animal, and no islet cells could be identified.

Concerning the Lipoids. Lipoidemia has long been known to be present in diabetes (see Kusunoki[9] for index to literature), and there is reason to suspect that it occurs frequently in advanced or serious cases. One of us (Williams) in a recent, not yet reported, study of 22 cases of advanced diabetes found the cholesterin content of the blood increased in 16 cases. We find in the literature, however, very few cases of diabetes that resemble ours in histopathology. As Anitschow[10] says, it is very desirable that such cases be reported. The first instance of large-cell hyperplasia in this disease which we have found was given by Schultze,[11] who, according to Anitschow,[12] would be entitled to priority in the matter. Schultze regarded the large cells of the spleen in his case as probably identical with those in Gaucher's disease. In this he was doubtless mistaken, for, according to modern views (see Mandlebaum and Downey[13 14]), these large cells in Gaucher's disease contain no lipoids. They were present in Schultze's case in large amount, and there was marked lipoidemia.

Later, Lutz[15] described 2 cases of lipoidemia in diabetes with similar hyperplasia of the spleen. The cells contained isotropic fat, mostly, but there was some in the anisotropic form. Although Lutz notes the marked similarity of the microscopic picture in his cases with that in Gaucher's disease, he did not claim that the pathological processes were identical. In the cases of Schultze and Lutz the liver, adrenals, and bone marrow were not said to be involved, though the lymph nodules were found by Lutz to contain large cells infiltrated with fat. They appeared to be desquamated endothelial cells.

These facts are enhanced in interest and importance when taken in connection with the effects of hypercholesterolemia, as reported by Anitschow, Chalatow, Krylow, Rothschild, Sternberg, Landau and McNee, Soper in Ziegler's *Beitr. z. path. Anat. u. allg. Path.*, 1913 and 1914, and by Adler,[16] Bailey,[17] Borberg[18] and others. While we cannot give an analysis of the literature in this article, we may state briefly that it has been shown by feeding animals with cholesterin for several months that a hyperplasia, with lipoid infiltration, can be produced in the spleen and bone marrow. The spleen hyperplasia is strikingly similar to that seen in the case of

[9] Ziegler's Beitr. z. path. Anat. u. z. allg. Path., 1914, lix, 564.
[10] Ibid., 1913–1914, lvii, 201.
[11] Verhandl. d. deutsch. path. Gesellsch., Strassburg 15 Tagung, 1912.
[12] Loc. cit.
[13] Loc. cit.
[14] Loc. cit.
[15] Ziegler's Beiträge, 1914, lviii, 273.
[16] Jour. Exp. Med., 1914, vol. xx.
[17] Ibid., 1916, xxiii, 69.
[18] Skand. Arch. f. Physiol., 1914, xxxii, 287.

diabetes which we have described in this paper. (Presumably the bone marrow in our own case would have shown the same pathological feature, but unfortunately we did not take a sample of the marrow, as we had no suspicion of hyperplastic change at the time the tissues were fixed.) Other interesting results of these experiments, such as atheromatous conditions of the aorta, were obtained by Anitschow and others. For these details the reader is referred to the papers above cited.

On the chemical side numerous studies are available in the works of the several authors mentioned above. From these investigations one sees that the tendency is more and more not to regard the regulation of the lipoid supply of the body as the function of any one organ, as, for instance, the liver, which has received so much attention in former years. It appears that the spleen, adrenals, and bone marrow, as well as the liver, play an important part; whether jointly or separately is not yet clear. Aside from its digestive function the pancreas may also contribute in some way. Aschoff has become so convinced of the interrelation of these organs that he regards certain endothelial structures in the bone marrow, spleen, and lymph nodes, and the stellate cells of Kupfer in the liver, together with the adrenal cortex, as the "endothelial metabolism apparatus," the conception being that it, as well as other tissues of the body, is concerned with the intermediate metabolism of cholesterin (Landau[19]). English authors, *e. g.*, Dorie, Ellis, Fraser and Gardner,[20] believe that a "cholesterin balance can be maintained in the body by the food intake." Certain French writers (Chauffard and others) think that the adrenals secrete cholesterin (see Rothschild[21]). They stand practically alone in this view. (For recent discussion of the subject see Rothschild's papers[22]). Ciaccio[23] lays stress on the apparent relations of the lipoids, phosphatids, cholin, and glycerin esters. He thinks they have a complex history in the adrenals and other organs.

Another statement bearing on the question of fat metabolism may be made in this connection. In regard to the causes of fatty infiltration (and degeneration), Fischer and Hooker[24] make an attractive suggestion in a recent article on the physical chemistry of emulsions. They hold that an important factor in the stabilizing of an emulsion is the state of the colloid that may be the emulsifying agent. A fat emulsified in a hydrated colloid may be made to separate out by altering the hydration capacity of the colloid by acids, or, in some instances, by alkalies. Fischer and Hooker believe that fat in tissue

[19] Ziegler's Beiträge, 1914, lviii, 667.
[20] Proc. Roy. Soc. (Biology) London, 1908, pp. 212, 227; 1908, pp. 109, 129, 230, 505; 1910, p. 559; 1912, p. 461.
[21] Ziegler's Beiträge, 1914, lx, 39.
[22] Ziegler's Beiträge, 1914, vol. lx.
[23] Arch. f. exp. Pathol. u. Pharmacol., 1915, lxxviii, 347.
[24] Science, 1916, N. S., xliii, 468.

cells is thus emulsified, and that it may appear in visible form when the hydration capacity of the tissue colloids is decreased. Hence, according to this view, a fatty infiltration may have an entirely different cause from those ordinarily offered. Might not the acidosis of diabetes favor this phenomenon of the appearance of lipoids in the tissue cells and blood in this disease?

In conclusion, one sees there is a tendency on the part of not a few writers to build up a polyglandular theory of fat metabolism similar to that proposed by von Noorden and others to explain the control of the carbohydrates in the body. This theory regarding the carbohydrates and the origin of diabetes has been somewhat discredited by Minkowski, Opie, and Allen.[25] Nevertheless, a close correlation of organs by hormones or other bodies is a fundamental point in physiology, and one to be taken into account, along with other factors in considering any disorder of metabolism.

The whole question of fat metabolism is in need of much further study, which must not overlook the importance of the carbohydrates, for, as Bloor[26] states in a recent contribution to the subject of fat assimilation, sugar appears to be necessary in some stage for complete combustion in the oxidation of fats.

From studies, with the more refined technic of the present day, we may expect to see rapid progress toward a clear understanding of the etiology and pathology of diabetes.

SUMMARY. A case of fatal diabetes with large-cell hyperplasia of the spleen, lymph nodes, and liver is presented. It is the fourth case on record so far as the authors can tell. Other cases have doubtless occurred, but the hyperplasia has been overlooked. It is highly desirable, therefore, that thorough autopsies be made whenever possible. The spleen, lymph nodes, adrenals, liver, and bone marrow especially should be examined, microscopically and with the polariscope, to determine the nature of the cell contents.

The hyperplasia in the case described, and in the other cases reported, has some resemblance to the cell changes in Gaucher's disease of the spleen. In this disease lipoids are absent in the large cells, which, furthermore, have characteristic histological features. Moreover, Gaucher's disease is a familial disorder.

It is shown that overfeeding with fat increases acidosis in diabetes and probably bears some relation, as yet not understood, to lipoidemia. The acidosis is readily controlled, as Allen and Joslin have shown.

A brief discussion of some of the newer ideas regarding fat metabolism is given.

We wish to make acknowledgments to Professors B. F. Kingsbury and S. H. Gage for assistance with the photographs.

[25] Glycosuria and Diabetes, 1913, p. 842.
[26] Jour. Biol. Chem., 1916, xxiv, 447.

RENAL GLYCOSURIA.

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and

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During the past summer the writers were engaged in a study of the influence of alkali, administered by duodenal tube, upon the glycosuria and hyperglycemia of human diabetes.[1] Among the cases which presented themselves was the following:

Case History.—Frank B., a poorly nourished young man, aged twenty years, was admitted to Bellevue Hospital on June 28, 1916. His family history was negative for tuberculosis and diabetes. He had had measles only as a child, and had always been strong and well up to the present illness, which began in November, 1914, with pains in his abdomen and epigastrium after meals. He also had furuncles, polyuria, and thirst, and became very weak in spite of a good appetite. He lost ten pounds in one month. He was then told by physicians that he had diabetes, and went to a hospital, where he was dieted, leaving the hospital sugar-free. Since that time he had been eating very little starch and no sugar. His urine was examined in October, 1915, and sugar was present. Since June 1, 1916, he had lost more weight and felt extremely tired. Upon admission to the hospital his thirst was not excessive, and he had no polyuria or infections.

His physical examination was negative, except that his tongue was slightly reddened and his breath gave a faint odor of acetone. The reflexes were a little sluggish.

On July 2 the patient was placed on a restricted diet containing 50 grams of carbohydrate, with a total food intake of about 35 calories per kilo. On the second day of this diet he excreted 24 grams of glucose. When the diet was changed (see table) so as to contain 15 grams of carbohydrate, he continued to excrete the same amount of sugar. By this time we had already suspected the nature of the glycosuria. Examination of the blood-sugar at 11 A.M., five hours after breakfast, revealed a normal percentage on several days. The diet was continued, with but slight variations, for eight days, and throughout this period the amount of sugar excreted did not vary more than 2 grams from a mean of about 26 grams daily, which was 11 grams more than the food contained. He was evidently also in minus nitrogen balance, for the urine alone contained some 4 to 6 grams more of nitrogen than did the food. Of this amount

[1] Murlin and Craver: Jour. Biol. Chem., December, 1916, vol. xxvii.

5 per cent. was ammonia nitrogen. The degree of acidosis, therefore, was mild.

When the carbohydrate in the food was increased to 100 grams, mainly by the addition of oatmeal, the excretion rose on the first day 10 grams, the next day 6 grams more, and then it returned in two days to about its former level. During the last four days of this period it fell 3 or 4 grams below this level. The blood taken at the same time of day continued to show a normal percentage.

CASE I.—FRANK B.

Date.	Weight, kilos.	Food.				Urine.						Blood sugar, per cent. by weight.
		Total calories.	Carbohydrate, grams.	Fat, grams.	Food nitrogen, grams.	Volume, c.c.	Specific gravity.	Acidity, c.c. N/10.	NH_3—N.	Total nitrogen, grams.	Glucose, grams.	
July												
2–3	58.2	1847	50.5	139.9	13.6	1106	1032	510	0.60	15.49		
3–4	57.7	1896	50.5	142.1	15.2	1360	1028	602	0.66	18.91	23.8	
4–5	57.2	1903	14.9	147.5	19.2	2094	1023	785	0.86	22.98	24.2	
5–6	56.9	1895	14.9	158.8	20.8	1895	1027	853	1.03	24.91	27.1	0.097
6–7	56.7	2020	14.9	156.7	20.4	1705	1028	904	1.28	26.66	28.1	
7–8	56.4	2046	14.9	158.2	20.4	1745	1025	873	1.43	26.90	25.8	0.105
8–9	56.3	2064	14.9	159.2	20.8	1337	1032	769	..	25.4	27.9	
9–10	56.8	2064	14.9	159.2	20.8	1770	1024	717	..	24.5	26.0	0.102
10–11	56.5	2222	14.9	171.3	22.6	1845	1023	756	..	24.5	25.7	
11–12	55.8	2224	14.9	171.0	22.3	1330	1029	745	..	24.1	24.0	
12–13	56.2	2592	100.4	170.7	23.5	1620	1027	753	..	24.1	34.1	
13–14	55.8	2262	100.4	153.5	16.8	1024	1036	655	..	16.9	39.8	0.091
14–15	56.5	2262	100.4	153.5	17.4	1535	1026	629	..	14.7	35.0	
15–16	56.2	2262	100.4	153.5	16.8	1850	1022	620	..	17.6	30.6	0.081
16–17	56.1	2245	100.4	153.1	16.4	1815	1020	560	..	17.2	25.0	
17–18	55.9	2262	100.4	153.5	16.8	2125	1016	537	..	15.8	19.2	0.085
18–19	56.1	2254	100.4	153.7	16.4	1565	1023	614	..	16.6	22.3	
19–20	56.2	2261	100.4	153.7	17.4	1710	1022	654	..	16.7	24.4	0.092
20–21	56.1	2261	100.4	153.7	16.5	1280	1028	589	..	16.1	22.6	0.08
27–28	..	..	General ward diet			1850	..	..	..	..	34.4	
Aug.												
23–24	..	Practically unrestricted diet				1200	1033	726	..	19.6	30.9	
24–25	..	..	Fasting.	..	..	..	..	..	..	..	0.0	

The characteristics of renal glycosuria have been succinctly stated by Allen[2] as "glycosuria, with normal glycemia, relatively independent of diet." It is evident that the case described fulfils this definition precisely. In its chemical aspects it very closely resembles the case recently described by Lewis and Mosenthal.[3] With from 14 to 270 grams of carbohydrate in the diet the excretion of sugar in their case varied between 4.3 and 27 grams, the blood-sugar being normal.

There is one difference, however, which may be worthy of note, though we are not certain that it has any significance for this type of malady—namely, whereas it required six days of starvation to clear away sugar from the urine in their case, in ours it required only one day. At this time the young man had been living in the

[2] Glycosuria and Diabetes, Boston, 1913, p. 544.
[3] Bull. Johns Hopkins Hosp., 1916, xxvii, 133.

country and working as a gardener for one of the writers for about a month following the termination of the observations made in the hospital. He had improved markedly in strength, beginning with light work and increasing until he was able at the time mentioned to mow a rather large lawn without undue fatigue. On a diet containing oatmeal for breakfast, one slice of bread at each meal, and two glasses of milk, besides green vegetables and plenty of meat, his urine contained only 30.9 grams of glucose. This was the day before fasting. The fasting urine, begun at 7 A.M., twelve hours after his last meal, contained only the faintest possible trace of glucose, not more than is often found in normal urines.

The patient returned to the city October 1, 1916, and found work as a street-car conductor. His urine at this time contained a considerable amount of sugar, which was not quantitatively estimated.

CLINICAL STUDIES OF ACIDOSIS.

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and

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During the past few years much progress has been made in the study of the regulation of the body fluids as regards acidity and alkalinity and in the development of our conception of the condition known as acidosis.

Acidosis may well be compared with disturbance of the body temperature. It is recognized that life can continue only within a limited range of temperature variation and that health is compatible only with a still more restricted range. We are, more or less, familiar with the mechanisms which regulate the body temperature and maintain its constancy. Similarly, we have learned that the reaction of the body fluids as regards acidity and alkalinity must possess a degree of constancy even greater than must their temperature, if a normal condition or, indeed, life itself is to continue. Largely through the work of Lawrence Henderson,[1] and

[1] Clinical Studies on Acid Base Equilibrium and the Nature of Acidosis, Arch. Int. Med., 1913, xii, 153. Sellards, A. W., the Determination of Equilibrium in the Human Body between Acids and Bases, with Especial References to Acidosis and Nephropathies, Bull. Johns Hopkins Hosp., 1912, xxiii, 289.

his associates we have become familiar with at least some of the mechanisms by which this reaction is kept constant. The normal reaction in the body is maintained chiefly by three means: The first of these is the presence in the blood and lymph of the salts, chiefly the sodium salts, of two very weak acids, carbon dioxide and phosphoric acid. Of these two acids the former is the more abundant and important. In the blood and lymph, sodium carbonate (alkaline) and carbon dioxid (acid) are both present in such proportion as to give a nearly neutral reaction. Similarly disodium hydrogen phosphate (alkaline) and monosodium phosphate (acid) are both present in the proportions to give the same nearly neutral reaction. If to this almost neutral fluid a stronger acid, such as oxybutyric or lactic or hydrochloric acid be added, there occurs an interchange which diagrammatically may be expressed as follows: Each unit of strong acid combines with sodium of the salts of these weak acids, thereby liberating one unit of weak acid for each unit of strong acid introduced.

Sodium phosphate + hydrochloric acid = sodium chloride + phosphoric acid.

Sodium carbonate + hydrochloric acid = sodium chloride + carbon dioxid.

Thus for every unit of strong acid introduced into the blood there is liberated a unit of weak acid which possesses much less power of altering the reaction of the blood. The capacity of a free acid in a given concentration to alter the reaction of a fluid is dependent upon its ionization. For example, in a decinormal solution of hydrochloric acid, 91 per cent. of the hydrogen is dissociated in aqueous solution at ordinary temperature. Thus: $1000\ HCl = 910\ \overset{+}{H} + 910\ \overset{-}{Cl} + 90\ HCl$; on the other hand, in a decinormal solution of acetic acid only 1.3 per cent. of the reacting hydrogen is dissociated under similar conditions. Thus: $1000\ H(C_2H_3O_2) = 13\ \overset{+}{H} + 13\ \overset{-}{C_2H_3O_2} + 987\ H(C_2H_3O_2)$. Hence, a decinormal solution of hydrochloric acid although containing the same amount of reacting hydrogen as a decinormal solution of acetic acid is seventy times as strong an acid as the acetic acid, because the hydrogen ion concentration of the hydrochloric acid is seventy times as great as that of the acetic acid. The reaction, the color of an indicator added to a solution and in general the properties which we group under the term acidity are dependent upon the hydrogen ion concentration of the solution.

For the purpose of denoting the hydrogen ion concentration or reaction of a solution the notation now generally used in medical work is the logarythmic notation. In this notation the hydrogen ion concentration of a neutral solution is about 7; increasing degrees of acidity are indicated by decreasing figures and increasing degrees of alkalinity by increasing figures. By this notation the reaction of

urine ranges, according to Henderson and Palmer,[2] depending upon the character of the diet and other factors between the acid urine 4.7 and the alkaline urine 8.7. As a rule, it lies between 5 and 7.5. The blood possesses a very constant reaction at 7.4.

The first factor, therefore, in maintaining the constancy of reaction of the blood is the presence of considerable amounts of sodium carbonate with carbon dioxid and of sodium phosphate in the blood. When acids are added to the blood they combine with this sodium and liberate carbonic and phosphoric acids, both having very low coefficients of dissociation, hence producing a minimal change in the hydrogen ion concentration of the blood. This factor alone is extremely potent in diminishing the changes in the reaction of the blood and body fluids when subjected to the addition of acids or alkalies. The second and third factors are the rapid elimination from the body of these weak acids when so liberated, the phosphoric acid being eliminated by the kidney and the carbonic acid by the lungs. To these weak salts constituted with the weak acids, the sodium phosphate and sodium carbonate, Henderson has given the name "buffer substances," because of their effect in limiting the changes in reaction that would follow the introduction of acids or alkalies into the blood. As a result of their presence in the body fluids and of the rapid elimination by the lungs and kidneys of the carbonic acid and phosphoric acid liberated from them the blood and body fluids always preserve that constancy of reaction essential to life. It must be clear, however, that the continued introduction of acids into the blood will tend to reduce the amount of these buffer substances available, and must invariably do so if their depletion exceeds the body's capacity for replacing them. When such a reduction in the buffer substances of the blood has occurred the condition is that known as "acidosis." Acidosis may be defined as any condition in which the buffer substances of the blood and body fluids are reduced below the normal. The primary effect of such a reduction is a diminution in the capacity of the blood to transport acids or alkalies. The acid most abundantly produced in the body is carbonic acid, and when there is a reduction of the buffer substances of the blood there is a reduction in the blood's capacity for carrying carbonic acid. If this be marked enough there occurs an accumulation of carbonic acid in the tissues, and among other tissues in the respiratory center. As is well known, any increase of the acidity in the respiratory center, such as will be induced by an accumulation of CO_2, serves as stimulant to this center. A more thorough ventilation of the lungs results. A more thorough ventilation of the blood follows, and this favoring the removal of the CO_2 from the tissues, limits its further accumulation. Hence, an equilibrium

[2] Extreme Variations of the Concentration of Ionized Hydrogen in Human Urine, Jour. Biol. Chem., 1913, xiv, 81.

is established as a result of the response of the respiratory center to the carbon dioxid stimulation, and there is maintained an increased respiratory activity with more thorough ventilation of the lungs. This adjustment gives us one clinical symptom of acidosis, namely, hyperpnea, and one of our laboratory methods for detecting acidosis, namely, the reduction in the carbon dioxid concentration of the alveolar air; the latter, of course, being used as a measure of the thoroughness of pulmonary ventilation. Since the carbon dioxid tension of the alveolar air is, at least under normal conditions of the lungs, equal to the carbon dioxid tension of the arterial blood leaving the lungs, this increased ventilation of the lungs with lowering of the carbon dioxid tension of the alveolar air leads also to a lowering of the carbon dioxid tension of the arterial blood. It is well to emphasize the distinction between carbon dioxid tension and carbon dioxid content of a fluid or atmosphere. Like any other gas, carbon dioxid, whether in the air or dissolved in fluid, is present at some definite pressure or tension. In air the relation between the percentage of carbon dioxid and its pressure or tension is a simple one. Its pressure bears the same proportion to the total pressure of the air that its volume does to the total volume of the air. Thus, if carbon dioxid constitutes 6 per cent. of a sample of air, and that air is at atmospheric pressure (barometric pressure), which at the time is, let us suppose, 765 mm. of Hg., then the carbon dioxid tension in the sample of air will be 6 per cent. of 765, or 45.9 mm. Hg. The carbon dioxid of the alveolar air may be expressed either in per cent. or in mm. of Hg. tension, usually the latter. The carbon dioxid tension of a fluid is the pressure which the carbon dioxid exerts at the surface of the fluid. It is measured by determining the carbon dioxid which must be maintained in an atmosphere in contact with the fluid in order to keep the carbon dioxid content of the fluid unchanged. If the carbon dioxid tension of the atmosphere contiguous to a fluid is greater than that of the fluid the fluid absorbs carbon dioxid until the tension in each is equal, and *vice versa*. The amount or percentage of carbon dioxid, however, which a fluid must contain to possess a certain carbon dioxid tension varies greatly, depending upon the nature and temperature of the fluid. This is illustrated in the following table, giving the approximate carbon dioxid content and carbon dioxid tension of distilled water, a sample of blood and of serum at 38°. If acid be added to any fluid the carbon dioxid content of the fluid will be decreased for any given carbon dioxid tension. Reduction of the temperature increases the carbon dioxid content for any given carbon dioxid tension.

It is, of course, the carbon dioxid tension, not content, of alveolar air and of arterial blood which are equal. In some of the discussions of this subject it has been stated that in acidosis the carbon dioxid tension of the blood is decreased. This statement is open to criticism. In acidosis the total carbon dioxid content of the

blood (carbonate plus free carbon dioxid) is decreased; the amount of CO_2 that the blood can carry at a given CO_2 tension is decreased. As a result of stimulation of the respiratory center the pulmonary ventilation is greater, hence the CO_2 tension of the alveolar air and hence of the arterial blood is lower than normal; but, however much the total carbon dioxid content of the blood, arterial and venous, is reduced following the introduction of acids into the blood, and however much the carbon dioxid tension of the arterial blood is decreased by the increased respiratory activity, there is no proof that the carbon dioxid tension of the venous blood is decreased; indeed, it is possible that it may even be increased. Adequate studies upon this point are difficult, and are not yet available. Until the last few months only the very indirect method of gauging the existence of acidosis, namely, the determination of the thoroughness of pulmonary ventilation by estimating the carbon dioxid content or tension of the alveolar air, was our best laboratory method for the recognition of acidosis. The technic of this method has been greatly simplified recently by Marriott,[3] so that it may be carried out at the bedside in about five minutes' time and without any complicated apparatus. The value of this method has always been limited, however, first, by the fact that as a guage of the state of the blood it is dependent upon a normal irritability of the respiratory center. A hyperirritability of the respiratory center will maintain an increased pulmonary ventilation and a lowered alveolar CO_2 content without there being any acidosis, and conversely a diminished irritability of the respiratory center may diminish the evidence by this method of an existing acidosis. In the second place an alteration in the pulmonary ventilation may readily occur from unintentional alteration by the patient of his manner or rate of breathing during the time of examination. Moreover, in certain conditions, such as Cheyne-Stokes breathing, the pulmonary ventilation is variable and in pulmonary disease, such as pneumonia, we do not yet know what effect the local disease has upon the relation between the pulmonary ventilation and the state of the blood.

AMOUNT OF CO_2 IN VOLUMES PER CENT. HELD IN DISTILLED WATER, IN A SAMPLE OF WHOLE BLOOD (BOHR) AND IN A SAMPLE OF SERUM (JACQUET) AT THE SAME TEMPERATURE, 38°, AND THE INDICATED CO_2 TENSIONS.

CO_2 tension in mm. Hg.	Volumes per cent. of CO_2 in		
	Water, per cent.	Whole blood, per cent.	Serum, per cent.
15 mm.	1.1	30.5	47.2
30 mm.	2.2	38.9	62.1
50 mm.	3.7	45.3	64.6

Fortunately, for the progress of our knowledge of acidosis, two methods have been given us during the past year which enable

[3] The Determination of Alveolar Carbon Dioxid Tension by a Simple Method, Jour. Am. Med. Assn., 1916, lxvi, 1594.

us to study directly from the blood itself the "buffer value" of the blood. The first devised by Van Slyke, Stillman, and Cullen[4] is a method for measuring directly by means of a special gas buret the amount of the sodium carbonate buffer in the blood. The second, devised by Levy, Rowntree, and Marriott,[5] is a method for gauging the same factor indirectly by determining the hydrogen ion concentration of a sample of the blood under certain conditions.

The first of these methods has been used by us in a series of clinical cases, and the results of these studies are here presented, together with some considerations concerning certain features of the technic.

The principle of this method is to obtain blood from the patient, oxalte it, separate the plasma and subject the latter to an atmosphere of definite carbon dioxid content or tension, about 6 per cent. (45 mm. tension). When the plasma has been brought into equilibrium with this atmosphere 1 c.c. of the plasma is transferred to a special gas buret, and by means of acid and a vacuum all the CO_2 held as carbonate is liberated and the total CO_2 drawn from the plasma into the vacuum and measured. The total CO_2 content after reduction to 0°, 760 mm. pressure, and correction for vapor tension, may be expressed as volumes per cent. of the original plasma. Thus, 1 c.c. of normal human plasma so treated will yield about 0.70 c.c. of CO_2, or seventy volumes per cent.

Technic. Upon first using this method we employed oxalated plasma obtained in the usual way by centrifuging the oxalated blood in open centrifuge tubes. The results secured were frequently surprising, however, and especially the remarkable variations often observed in repeated examinations of the blood of the same individual at different times. Investigation of the various steps in our procedure showed that these irregularities were due to the fact that the carbon dioxid binding capacity of a plasma is greatly influenced by the carbon dioxid tension present in the whole blood at the moment the cells and plasma are separated. If the carbon dioxid tension of the whole blood be high at the time of the separation into cells and plasma the plasma will have a higher binding capacity for carbon dioxid at any given tension than if the carbon dioxid tension of the whole blood be low at the time of the separation. This relation first pointed out by Zuntz[6] has been subsequently more thoroughly investigated by Guerber[7] and Petry.[8]

[4] Nature and Detection of Diabetic Acidosis, Proc. Soc. Exper. Biol. and Med., 1915, xii, p. 165.

[5] A Simple Method for Determining Variations in the Hydrogen ion Concentration of the Blood, Arch. Int. Med., 1915, xvi, 389.

[6] Bohr, C., Blutgase und respiratorischer Gaswechsel. In Nagel, W.: Handb. der Physiol. des Menschen, 1905, i, 116. Zuntz: Beiträge zur Physiologie des Blutes, Inaug. Diss., Bonn, 1868.

[7] Ueber den Einfluss der Kohlensäure auf die Verteilung von Basen und Säuren zwischen Serum und Blutkörperchen, Sitzbericht. d. phys. med. Gesellschaft z. Wurzburg, 1895–96, p. 28.

[8] Ueber die Verteilung der Kohlensäure im Blute, Beiträge z. chem. Phys. und Path., Hofmeister, 1902–3, iii, 247.

By these observers it was shown that when CO_2 escapes from the plasma of whole blood and leaves behind the base chiefly sodium, with which it has been combined, thus increasing the alkalinity of the plasma, a diffusion of hydrochloric acid occurs from the cells into the plasma to combine with at least a part of this free base. If this plasma is now separated from the cells its combining power for CO_2 is obviously less than that of the original plasma, since a portion of its base originally capable of holding CO_2 is now combined with hydrochloric acid diffused from the cells. When the whole oxalated blood is drawn and centrifuged in the ordinary way in open tubes a variable escape of CO_2 occurs during the process, and consequently from the same portion of blood, plasmas of very different binding capacities may be secured. It is in our experience highly important that either the escape of CO_2 from the blood be prevented from the time the blood is drawn until the removal of the plasma from the cells, or else that the blood be brought to some standard carbon dioxid tension at the time of centrifuging and kept at this tension until the plasma is separated. We are indebted to Dr. Van Slyke[9] for the suggestion of a simple method for securing the former of these two conditions. This consists of drawing the blood directly from the patient's vein through tubing which passes to the bottom of a centrifuge tube containing a few oxalate crystals and which ends beneath a layer of paraffin oil. The oil floating above the blood effectually prevents the escape of CO_2 until the centrifuging is complete and the plasma pipetted off. This paraffin oil method has been our standard method in these studies. In some cases, however, we have also saturated the whole oxalated blood at a tension of 6 per cent. CO_2 and kept it at this tension by stoppering or by covering with paraffin oil during the centrifuging.

To show the importance of this step we obtained in a series of seventeen cases the oxalated plasma from the whole blood in three ways: (1) blood drawn from the vein directly into a centrifuge tube beneath paraffin oil and hence protected from loss of CO_2 until removal of the plasma; (2) blood drawn and oxalated, exposed to the air, but subsequently saturated at 6 per cent. CO_2 tension and kept at this tension during centrifuging; (3) blood drawn, oxalated, and centrifuged in the ordinary way exposed throughout to the air. The plasmas obtained in these three ways were all saturated at 6 per cent. CO_2 tension and analyzed for their CO_2 content by Van Slyke's method. The results are shown in Table I, A. It will be seen that the paraffin oil and the 6 per cent. saturation of the whole blood give closely parallel results, the latter, as a rule, yielding a plasma that holds from 3 to 6 more volumes per cent. of CO_2. On the other hand the exposed blood

[9] Personal communication.

invariably yields a plasma of lower binding capacity, but in different individuals or in the same individual at different times the resulting plasma may be only one volume per cent. lower, or as much as 24 volumes per cent. lower.

TABLE I.—PART A.—THE EFFECT OF THE CO_2 TENSION OF THE WHOLE BLOOD UPON THE CO_2 CAPACITY OF THE PLASMA DERIVED FROM IT.

	CO_2 content of plasma saturated at 45 mm. CO_2 tension, the whole blood having been				
Case No.	Kept under paraffin oil.	Saturated at 45 mm. CO_2 at 20° C.		Exposed to air.	
	P.	S.	S–P.	E.	P–E.
1	73	77	4	50	23
2	73	72	–1	51	22
3	70	66	–4	68	2
3	66	68	2	49	17
4	66	70	4	49	17
5	65	68	3	49	16
6	64	73	9	48	16
7	64	68	4	57	7
8	64	68	4	43	21
8	62	68	6	50	12
9	62	68	6	59	3
10	60	64	4	55	5
11	59	62	3	38	21
12	53	59	6	43	10
13	52	58	6	44	8
14	51	49	–2	38	13
14	46	48	2	45	1

If the oxalated blood before centrifuging be thoroughly aerated by being poured from beaker to beaker for five minutes the resulting plasma exhibits a still lower CO_2 capacity, as shown in Table I, B.

PART B.

Case No.	Kept under paraffin oil. P.	Aerated 5 minutes A.	P–A.
15	70	48	22
16	70	59	11
17	66	47	19
18	65	46	19
19	64	49	15
20	61	44	17
21	58	51	7

At first sight it might seem surprising that saturation of the whole blood at 6 per cent. (45 mm.) CO_2 tension should increase the CO_2 capacity of the plasma as compared with the blood as drawn from the vein under paraffin oil. That this occurs is due to the fact that the saturation of the whole blood at 45 mm. tension was carried out at room temperature (18° to 20° C.), and the blood will, as a rule, hold more CO_2 at 18° C. at 45 mm. tension than at the same or higher tension that exists in the veins at 37° C.

Effects of Cyanosis. In considering the relative merits of the paraffin oil method and the 6 per cent. saturation of the whole

blood in the study of acidosis it will be recognized that most factors will alter the plasma in the same direction and about equally whichever of these methods be used. One conspicuous exception to this relation exists, however, namely, any alteration in the CO_2 tension of the venous blood as drawn, such, for example, as occurs in asphyxia or cyanosis. This may be seen in the experiments shown in Table II.

TABLE II.—EFFECT OF INJECTION OF ACID, ALKALI, AND OF ASPHYXIA ON THE CO_2 CAPACITY OF THE PLASMA.

Dog No.	Blood drawn after:	CO_2 content of plasma saturated at 45 mm. CO_2 tension, the whole blood having been		
		Kept under paraffin oil.	Saturated at 45 mm. CO_2 at 20° C.	
		P.	S.	S - P.
1	Control period . . .	54	56	2
	KH_2PO_4	47	52	5
	Asphyxia	48	46	-2
	Na_2CO_3	67	70	
2	Control period . . .	52	62	10
	Asphyxia	55	58	3
	KH_2PO_4	48	58	10

These experiments were performed to show the effect upon the CO_2 binding capacity of the plasma of injection of alkalies, of injection of acids, and of increase in the CO_2 tension of the venous blood from asphyxia.

EXPERIMENT I. A normal dog, weighing 10 kilos, was etherized; 10 c.c. of blood drawn and oxalated under paraffin oil from the right jugular vein and immediately a second portion of 10 c.c. drawn and oxalated exposed to the air for subsequent saturation as whole blood at 6 per cent. CO_2 (control blood). There was then injected in the course of fifteen minutes 150 c.c. of KH_2PO_4 solution (13.6 gms. per liter) into the left femoral vein. Two portions of blood were immediately taken from the right jugular vein as before (KH_2PO_4 blood). The trachea was then compressed until the tongue was deeply cyanosed and two more portions of blood taken as before from the right jugular vein (asphyxia blood). After a few minutes' interval 150 c.c. of 3 per cent. Na_2CO_3 solution was injected in fifteen minutes into the left femoral vein and two portions of blood taken as before from the right jugular vein (Na_2CO_3 blood). The injection of acid phosphate reduced the CO_2 capacity of the plasma obtained both by the paraffin oil and by the 6 per cent. saturation method. Asphyxia still further reduced the CO_2 capacity of the plasma by the 6 per cent. saturation method, but slightly increased that of the plasma from the paraffin oil method. Thus a slight acidosis of asphyxia was wholly obscured by the increased CO_2 tension of the venous blood when the plasma was obtained by the paraffin oil method.

EXPERIMENT II. This experiment is identical, except that the asphyxia was performed before the injection of the acid phosphate.

The results are similar, but perhaps even more striking. Whether this effect of asphyxia upon the plasma obtained by the paraffin oil method would ever be of clinical importance is not certain, but in a very cyanotic patient it is possible.

Van Slyke Method in Clinical Cases. A series of clinical cases chosen more or less at random have been studied by the Van Slyke method, using the paraffin oil method for obtaining the plasma. The results are shown in Table III. Throughout this study all figures are the volumes of CO_2 per cent. reduced to 0° C., 760 mm. and corrected for vapor tension. It has seemed to us that the normal limits by this method may be considered as lying between 65 and 80 volumes per cent. Between 55 and 65 volumes per cent. the patients have been, as a rule, mildly nephritic, mildly diabetic, or markedly arteriosclerotic, and might, therefore, be expected to exhibit the slightest grade of acidosis. Below 55 the patients have been for the most part advanced nephritics, except for one moderately severe diabetic and one quite septic case.

Comparison of Three Methods. In a series of cases we have compared the carbon dioxid capacity of the plasma obtained under paraffin oil, the alveolar air, using the Plesch-Higgins method[10] and the hydrogen ion concentration of the serum by the dialysis method of Levy, Rowntree, and Marriott after blowing off the free CO_2 from the dialysate as recently suggested by Marriott. The results are shown in Table IV. In general the results agree, but the method of Van Slyke is distinctly the most sensitive of the three and gives much more perfect duplicates than does the method of alveolar air.

Van Slyke Method Following Anesthesia. The Van Slyke method has been applied to the study of a few cases following nitrous oxide-ether anesthesia. The results are shown in Table V. It will be seen that after from thirty to one hundred and fifteen minutes, ether anesthesia, a lowering of the CO_2 capacity of the plasma, was constantly observed. The degree to which it was lowered was, in general, proportional to the duration of the anesthesia. In a thirty minutes' anesthesia the lowering was only two to four volumes per cent. while in an anesthesia of one hundred and five minutes it was reduced to forty-nine volumes per cent., about fifteen below the normal. The reduction is apparently at or near its maximum at the close of the anesthesia and exhibits no marked changes in either direction for the next four or five hours, perhaps for twenty-four hours. The time required for return to normal has not been determined.

In eight of ten cases in which the urine was studied, acetone was studied by the sodium nitroprusside test in the first or second twenty-four hours after operation. The ferric chloride test was positive once. Even when the acetone test was strongly positive, however, the total ketone bodies were never present in more than

TABLE III.—CLINICAL CASES. CO_2 CONTENT OF PLASMA (BLOOD TAKEN UNDER PARAFFIN OIL).

No.	Diagnosis.	Age.	Date.	Plasma CO_2.	Alveolar CO_2.	Blood-pressure.	Blood urea nitrogen.	Ketonuria gms. per 24 hours.
	Controls:							
1	Headache	.....	.....	78				
2	Carcinoma of lip	.....	.....	78				
3	Sprain	.....	.....	71				
4	Angioneurotic edema	.....	.....	71				
5	Sarcoma of leg	.....	.....	71				
6	Papilloma of bladder	.....	.....	70				
7	Pneumonia	.....	.....	69				
8	Varicocele	.....	.....	65				
9	Hemorrhoids	.....	.....	65				
10	Fracture of arm	.....	.....	65				
11	Myoma uteri	.....	.....	65				
12	Gastric neurosis	.....	Feb. 22	70				
	Gastric neurosis	.....	Feb. 26	64				
	Gastric neurosis	.....	Feb. 28	66				
13	Endothelioma	.....	Feb. 5	63				
	Endothelioma	.....	Feb. 8	65				
	Arteriosclerotics:							
14	Arteriosclerosis	57 years	.....	68	..	142–85	14	
15	Arteriosclerosis	60 years	.....	66	..	150–85		
16	Arteriosclerosis	49 years	.....	66				
17	Arteriosclerosis	59 years	Feb. 27	65	..	170–120	17	
			Mar. 9	71	..	170–120	29	
18	Arteriosclerosis	63 years	Mar. 16	61	..	230–130		
			Mar. 29	63	..	230–130		
19	Arteriosclerosis	56 years	.....	62	..	220–135	14	
20	Cerebral hemorrhage	.....	.....	60				
21	Atrophic cirrhosis	56 years	.....	57	..	160–120	13	
	Nephritics:							
22	Early nephritis	36 years	.....	72	..	176–110	17	
23	Chronic nephritis	42 years	.....	64	..	.....	33	
24	Early nephritis	24 years	.....	62	..	198–150	14	
25	Parenchymatous nephritis	21 years	Apr. 17	61	..	150–110	17	
			Apr. 19	63	..	150–110		
			May 6	64	..	150–110	16	
			May 15	69	48	135–90		
26	Chronic nephritis	15 years	.....	59	..	165–115	23	
27	Chronic nephritis	45 years	.....	59	..	185–135	18	
28	Acute nephritis	30 years	Apr. 12	53	30	115–65	35	
			Apr. 27	77	55	115–65	13	
29	Chronic nephritis	26 years	.....	53	..	140–100	21	
30	Advanced nephritis	44 years	Feb. 25	51	..	180–140	67	
			Mar. 4	46	..	180–140	49	
			Mar. 8	46	..	180–140	51	
31	Advanced nephritis	39 years	Apr. 17	48	..	.....		
			Apr. 27	55	..	.....	116	
			May 6	48	..	.....	119	
			May 12	46	35	.....	142	
32	Advanced nephritis	55 years	.....	37	33	190–100	122	
33	Advanced nephritis	56 years	.....	35	25	158–80	195	
34	Advanced nephritis	34 years	Mar. 27	40	..	178–115		
			Mar. 29	33	..	178–115		
	Mercurial nephritis:							
35	Bichloride poisoning (severe)	21 years	June 6	70	..	120–75	16	
			June 7	70	..	120–75	20	
			June 15	71	..	120–60	17	
36	Bichloride poisoning (mild)	24 years	June 12	70	..	115–70	14	
			June 15	70	..	120–75	13	
	Eclampsia:							
37	Eclampsia	.....	.....	57	..	.....	21	
38	Eclampsia	.....	.....	52	..	.....	29	
39	Eclampsia	.....	.....	52	35	.....	20	
40	Eclampsia	.....	.....	48	..	.....	13	
41	Eclampsia	.....	Mar. 28	46				
			Mar. 30	57	..	.....	14	
	Septic:							
42	Pelvic inflammation	32 years	Feb. 29	52	..	195–120	12	
			Mar. 27	63				
	Diabetes:							
43	Mild	48 years	.....	71	..	.....	....	2.0
44	Mild	25 years	.....	64	..	.....	....	0.4
45	Mild	51 years	.....	60	..	.....	....	2.0
46	Mild	35 years	Mar. 8	52	..	.....	....	4.6
			Mar. 29	64	..	.....	....	0.4

The blood urea nitrogen estimations in the table were performed by the urease method (Van Slyke and Cullen); the urinary ketones by Schaffer's method.

very small amounts, the largest amount excreted in twenty-four hours being 0.83 mgm. expressed as acetone (Shaffer's method). The total acid output by Henderson's and Palmer's method was normal.

TABLE IV.—COMPARISON OF CO_2 CONTENT OF PLASMA, CO_2 TENSION OF ALVEOLAR AIR AND HYDROGEN ION CONCENTRATION OF SERUM AFTER AËRATION OF DIALYSATE.

Case No.	CO_2 content plasma.	CO_2 tension alveolar.	Hydrogen ion of serum.
1	77	44	8.1
2	72	50	8.0
3	69	48	8.0
4	67	43	8.0–
5	65	50	7.9
6	64	39	8.0
7	63	41	8.0
8	62	38	8.1
9	58	44	8.1
10	52	40	8.0
11	52	35	7.9
12	46	35	7.9
13	37	33	7.7

TABLE V.—EFFECT OF ETHER ANESTHESIA ON CO_2 CONTENT OF PLASMA.

Case No.	Operation.	Age.	Duration of anesthesia, minutes.	CO_2 content: Before.	After.
1	Carcinoma of lip	72	30	73	69
2	Amputation of leg	17	30	70	66
3	Amputation of leg	30	30	65	63
4	Herniorrhapy	20	35	..	64
5	Hemorrhoids	19	35	65	59
6	Perineal, plastic	51	40	..	56
7	Nephrotomy	30	50	..	60
8	Ectopic pregnancy	35	50	..	53[10]
9	Nephrotomy	48	70	..	59
10	Perineal, plastic	46	85	..	47[10]
11	Suprapubic cystotomy	24	90	70	60
12	Pan hysterectomy	56	100	..	53[10]
13	Pan hysterectomy	58	105	..	51
14	Pan hysterectomy	19	105	..	49[10]
15	Pan hysterectomy	35	110	65	57
16	Gastrojejunostomy	39	115	..	56

Four of the patients received just at the close of the anesthesia two pints each of 5 per cent. glucose solution per rectum. These cases showed quite as marked a reduction of the carbonate content of the plasma as did comparable cases not receiving the glucose.

The cause of acidosis is different in different conditions. In diabetes it is due largely to the presence in the blood of the ketone acids. In nephritis and severe diarrhea it is probably, according to Howland and Marriott,[11] due to an impaired capacity on the

[10] Received glucose per rectum at close of anesthesia.

[11] Acidosis Occurring with Diarrhea, Am. Jour. Dis. of Child., 1916, xi, 309.

part of the kidneys to excrete phosphoric acid. For other types the cause of the acidosis is not known. That the clinical symptomatology varies somewhat with the type and cause of the acidosis is apparently true. Whether the treatment of acidosis, *per se*, apart from its cause will be of importance remains to be determined. Henderson has urged that in any conditions associated with reduction in the buffer value of the blood, sodium bicarbonate be given by mouth to the point of rendering the urine less acid, but not distinctly alkaline. Using this simple criterion one may endeavor to replenish the supply of buffer substances in the blood and yet avoid overtaxing the system with excessive alkali. In this connection attention may be called to the suggestion of Magnus-Levy[12] that in giving sodium carbonate solutions intravenously for the treatment of severe acidosis the injection of a highly alkaline solution may well be a severe insult to the system. He suggested that a safer plan is to pass CO_2 gas through the sterile sodium carbonate solution, to which a drop of phenolphthalein has been added, until the solution is colorless, when it becomes more closely analogous to the normal sodium carbonate-carbon dioxid buffer of the blood —the reaction of which is nearly neutral—the substance which one is aiming by such injections to replace.

Conclusions. 1. In the new methods for studying acidosis directly from the blood we have a means of investigation that constitutes a distinct advance upon our previous methods.

2. As criteria of the supply of "buffer substance" in the blood the carbon dioxid capacity of the plasma (Van Slyke, Stillman, and Cullen method) the hydrogen ion concentration of the serum (Levy, Rowntree, and Marriott method) and the alveolar air (Plesch-Higgins method) give results that are in general parallel. The first of these is the most sensitive of the three and gives much more satisfactory duplicates than does the alveolar air determination. It affords a simple and quick method of determining the presence and degree of acidosis.

3. In using the method for the CO_2 capacity of the plasma, and presumably in any method intended to measure directly or indirectly the alkalinity of the plasma, the CO_2 concentration of the whole blood must be kept unchanged or brought to a standard tension while centrifuging and separating the plasma from the cells.

4. Asphyxia or any condition of high CO_2 tension in the blood *in vivo* raises the CO_2 capacity of the plasma if the latter is separated by the paraffin oil method, and may interfere with the recognition of a slight acidosis. This may be overcome by saturating the whole blood at a standard CO_2 tension before centrifuging and maintaining this tension until the plasma is pipetted off.

[12] Ueber subkutane Infusionen von Mononatriumkarbonat, Therap. Monatsch., 1913, xxvii, 838.

5. By the Van Slyke method the normal CO_2 capacity of the plasma reduced to 0° 760 mm. pressure and correcting for vapor tension appears to be about sixty-five to eighty volumes per cent. This is slightly reduced in arteriosclerotic conditions and moderately to markedly reduced in diabetes and nephritis, especially in the advanced stage.

6. After ether anesthesia there is a depression of the CO_2 capacity of the plasma of from two to twenty volumes per cent. This depression is proportional to the duration of the anesthesia. The lowest figure observed was 47. This reduction is present and probably maximal at the close of the anesthesia, and apparently remains little altered for at least five hours. A single injection of two pints of a 5 per cent. glucose solution per rectum at the close of the anesthesia does not lessen the reduction in the CO_2 capacity during the next five hours.

THE TOXEMIAS OF PREGNANCY.

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Although no general agreement has been reached concerning the nature of the substances causing the toxemias of pregnancy, two explanations have claimed special consideration. Ewing and Wolf,[1] noting the anatomical changes of the liver in eclampsia, the facts that leucine and tyrosine had been reported in eclamptic urines, and that they themselves found often a decrease in urea and an increase in the "undetermined nitrogen" fraction of the urine, suggested that the amino-acids were incompletely catabolized in the degenerated liver, and were the cause of both the toxemia and the abnormal nitrogen distribution. Later Murlin and Bailey,[2] also working in the Cornell laboratory, attacked the same problem with the aid of Soerensen's formol titration method, which is specific for amines and amino-acids. They decided that not only the amino-acid fraction, but also the other nitrogen fractions of the urine are likely to be within the limits of normal variation both before and immediately after the convulsions of eclampsia, and that consequently the nitrogen distribution in the urine offers no reliable

[1] Am. Jour. Obst., 1906, lv, 289.
[2] Jour. Am. Med. Assn., 1912, lix, 1522.

means for either diagnosing the preëclamptic state or indicating the nature of the toxin.

The other explanation is that abnormal acids in the blood are responsible for the toxemia. It is known that even in normal pregnancy a slight degree of acidosis is indicated by the carbon dioxide content of the alveolar air,[3] and it was not illogical to suggest that an intensification of the acidosis might be a factor in the cause of eclampsia. Zweifel[4] not only designated acidosis as the cause of eclampsia, but identified the specific acid as sarcolactic. This he found to be three times as concentrated in blood from the umbilical cord as in the venous blood of the mother, and he interpreted the results as proof that the mother is intoxicated by lactic acid formed in the fetus. Hasselbalch and Gammeltoft[5] found also that in two out of four cases of eclampsia examined by them the "regulated" hydrogen ion concentration of the blood was abnormally high, the values for pH at normal CO_2 tension being 7.17 and 7.22 instead of the normal 7.45.

It seemed to the writers desirable to test the acidosis hypothesis quantitatively on a number of cases in order to ascertain whether a degree of acidosis unusual for pregnancy regularly accompanies eclampsia, and whether the intensity of the acidosis is sufficient to account for the symptoms and ultimate coma noted. It seemed also not without interest to test with the gasometric method the proportion of amino-acid nitrogen in the urine in eclampsia, since the results of previous investigations on amino-acids in the urines of pregnancy, which have been performed with the help of the formol titration method, have not been entirely in agreement. While Hasselbalch and Gammeltoft found the proportion of amino-acid nitrogen normal (2 to 3 per cent. of the total nitrogen) in normal pregnancy, Falk and Hesky, with the same method, report results running chiefly between 3 and 7 per cent., 73 per cent. of the cases showing figures above the ordinary limits observed in non-pregnant women. Falk and Hesky also noted in pregnancy a similar increase in peptide nitrogen, which varied from 2 to 7 per cent., non-pregnant women showing figures of from 1 to 2 per cent. Murlin and Bailey did not determine the peptide nitrogen, but found in their three cases of normal pregnancy amino-acid nitrogen figures of 3.3, 5.1, and 4.3 per cent. of the total nitrogen, figures which, like those of Falk and Hesky, are somewhat above the normal.

We have determined in the urine the "total amino-acid nitrogen,"[6] which includes the nitrogen of the free amino-acids and also that of the amino-acids conjugated in such forms as peptides and hippuric acid. In normal individuals this nitrogen runs from 1.5 to

[3] Hasselbalch, K. A., and Gammeltoft, S. A., Biochem. Ztschr., 1915, lxviii, 207.
[4] München. med. Wchnschr., 1906, liii, 297. [5] Loc. cit.
[6] Levene, P. A., and Van Slyke, D. D., Jour. Biol. Chem., 1912, xii, 310; 1913, xvi, 125.

3.5 per cent. of the total nitrogen. Consequently the excretion of any considerable amount of amino-acids either free or conjugated would cause a marked rise in this figure. We have also determined the proportion of the total nitrogen in the form of urea, ammonia, and albumin.

As a further index of the amino-acid metabolism we have determined in a number of cases the amino-acid nitrogen of the blood[7] since the blood can be expected, even before the urine, to show evidence of failure of the organism to metabolize amino-acids with normal efficiency. The total non-protein nitrogen and urea nitrogen were also determined in most of the blood analyses.

As a measure of acidosis we have determined the volume percentage of carbon dioxide bound in the form of bicarbonate by the blood plasma.[8] Since all the reserve alkali of the blood, *i. e.*, the alkali in excess of that combined with acids other than carbonic, takes the form of bicarbonate, this figure indicates the alkaline reserve of the blood plasma, and in fact of the body as a whole.

METHODS. Urea was determined in both blood and urine by Marshall's urease method in the form developed by Van Slyke and Cullen.[9]

Amino-acid nitrogen of the blood was determined after precipitation of the proteins by alcohol, as described by Van Slyke and Meyer.[10] The micro-amino apparatus was used, so that the determinations could be done on an amount of filtrate corresponding to 2 c.c. of blood. As shown by Greenwald[11] the proteins precipitated by alcohol adsorb a portion of the amino-acid nitrogen, but the proportion is so constant that for comparative purposes the method is accurate.

Total non-protein nitrogen of the blood was determined by Folin micro-Kjeldahl[12] determination on an aliquot portion of the alcoholic filtrate from the blood proteins.

Carbon dioxide capacity of the plasma was determined by Van Slyke's method.[13]

The albumin of the urine was determined by a modification of Welker's method[14] as follows: Twenty-five c.c. of urine were acidified with acetic acid and heated to coagulate the albumin. The volume of the solution was then brought to 50 c.c. by the addition of an aluminum hydroxide suspension, prepared as described by Welker for adsorption of proteins, and containing 0.5 per cent. of Al_2O_3. The mixture was shaken and filtered through a folded filter. The nitrogen content was determined by Kjeldahl on 4 c.c. of the

[7] Van Slyke, D. D., and Meyer, G. M., Jour. Biol. Chem., 1912, xii, 399.
[8] Van Slyke, D. D., Proc. Soc. Exper. Biol. and Med., April 21, 1915.
[9] Jour. Biol. Chem., 1914, xix, 211.
[10] Loc. cit.
[11] Jour. Biol. Chem., 1915, xxi, 61.
[12] Jour. Biol. Chem., 1913, xi, 529.
[13] Loc. cit.
[14] Tracy, G., and Welker, W. H., Jour. Biol. Chem., 1915, xxii, 55.

filtrate and on 2 c.c. of the untreated urine. The difference indicated the albumin nitrogen.

The use of the aluminum hydroxide alone, without previous coagulation of the mass of the albumin, proved insufficient to remove all the albumin from some of the urines in which it was especially abundant.

The total amino-acid nitrogen of the urine was determined on 25 c.c. of the albumin-free filtrate by the gasometric method previously described, the urea being destroyed and conjugated amino-acids set free by heating with dilute sulphuric acid in an autoclave.

The *ammonia* was determined by Folin's aëration method, 5 c.c. of saturated potassium carbonate solution being added to 5 c.c. of urine, and the ammonia aërated into 0.02 N hydrochloric acid.

Discussion of Results. *Acidosis.* Examination of between 20 and 30 normal plasmas by Van Slyke, Stillman, and Cullen,[15] and of 30 by Gettler and Baker[16] have shown that 100 c.c. of average normal plasma binds 65 c.c. of CO_2, no normal plasma showing a figure below 55 and very few above 75, the great majority lying in the range 60 to 70. Our 14 cases of normal pregnancy all showed figures below the average normal of 65, and 10 of them were observed on at least one day to show figures below the minimum normal of 55. Consequently we can agree with the conclusion reached as the result of their alveolar carbon dioxide determinations by Hasselbalch and Gammeltoft,[17] that a slight acidosis is usually present in even normal pregnancy.

Our cases of toxemia of both the eclamptic and vomiting type show little difference from normal pregnancy in their alkaline reserve. The same subnormal carbon dioxide is seen, but in no case does it approach so low a value as 30 c.c. of CO_2 per 100 c.c. of plasma, which experience with the acidoses of diabetes and nephritis indicates must be fallen below, before any but exceptional cases show serious distress from acidosis *per se*.

The blood from the umbilical cord showed a bicarbonate content in only one case significantly different from that of the mother's blood. The results give no support to the presumption that the fetus elaborates amounts of acid sufficient to cause acidosis in the mother.

It is noteworthy that although the cases of pernicious vomiting show strikingly high ammonia figures, the plasma bicarbonate indicates no greater degree of acidosis than may be observed in non-toxic pregnancy. A. W. Sellards[18] mentions similarly a case of toxemia of pregnancy in which 40 per cent. of the urinary nitrogen was ammonia, but in which other evidence excluded acidosis.

[15] Loc. cit.
[16] Jour. Biol. Chem., 1916, xxv, 211.
[17] Loc. cit.
[18] Johns Hopkins Hosp. Bull., 1914, xxv, 147.

Amino-acids. In only 3 of the 23 cases of toxemia in which amino nitrogen of the urine was determined was the figure above the 3.6 per cent., the maximum noted in a previous series of normal men. In the 3 cases where a higher figure was observed the amino nitrogen exceeded the usual limit by a margin smaller that the maxi-

TABLE I.—PLASMA BICARBONATE AND NITROGEN DISTRIBUTION OF URINE IN NORMAL PREGNANCY.

History.	Total N. g. per 100 c.c.	Urine. Per cent. of total N. as:					C.c. of CO_2 bound by 100 c.c. of plasma.	
Para, months pregnant, etc.		Albumin.	Urea.	Ammonia.	Total amino-acids.	Undetermined.	Mother's blood.	Infant's blood.
Full term	1.168	..	75.8	5.8	..	..	57	
Full term	1.014	..	83.8	5.8	3.7	6.7	60	
2 days p. p.	0.782	..	83.2	4.4	2.6	9.8	54	
Full term	0.596	..	69.2	7.0	5.4	18.4	51	
1 day p. p.	0.963	..	75.8	6.7	3.7	13.8	61	
Full term;	..	..	..	..	..	..	53	51
2d blood; 2 days p. p.							54	
Full term;	..	..	..	..	..	..	51	56
2d blood; 3 days p. p.							62	
Full term;	..	..	..	..	..	..	49	52
2d blood; 3 days p. p.							58	
Full term;	..	..	..	..	..	..	50	53
2d blood; 3 days p. p.							63	

TABLE II.—NITROGEN DISTRIBUTION OF BLOOD AND URINE IN ECLAMPSIA.

History.	Non-protein N. of blood. Mg. per 100 c.c.			Urine. Total N. g. per 100 c.c.	Per cent. of total N. as:				
Para, months pregnant, blood-pressure, etc.	Total.	Urea.	Amino acids.		Albumin.	Urea.	Ammonia.	Total amino acids.	Undetermined.
P. V, 8 mos., 230 b. p.; accouchment force; died, typical liver lesions	46	21	7.6	0.642	4.7	54.3	10.2	2.5	25.7
P. I, 8 mos., 248 b. p.; no convulsions nor coma; mild type	36	14	7.9	1.410	6.2	64.4	8.1	2.7	17.6
P. IV, 9 mos., 196 b. p.; semicomatose 7 days; died 5 days p. p.	31	10	7.9	0.784	20.9	46.1	3.1	3.2	26.7
P. I, 9 mos., 140 b. p.; semicomatose	26	15	4.0	0.610	10.1	56.2	3.2	2.5	28.0
P. I, 8 mos., 170 b. p.; marked edema	28	..	6.2	0.374	17.9	62.0	6.6	2.0	11.5
P. I, 7 mos., 170 b. p.; edema	25	..	7.8	1.195	4.1	66.2	10.1	2.3	17.3
P. I, 9 mos., 180 b. p.; no convulsions	28	..	5.0	0.633	16.3	51.2	10.2	3.1	19.2
P. I, 8 mos., 150 b. p.; died in coma, 6 days p. p.; first urine and blood 4 days p. p.; second 5 days p. p.	43	26	4.4	1.887	1.1	74.0	5.6	2.0	17.3
				2.275	7.7	72.0	4.6	1.5	14.2
P. I, 9 mos., 125 b. p.; moderate edema; coma; first specimen day of delivery; second one day p. p.	41	25	5.5	0.680	9.7	53.0	12.0	4.7	20.6
	41	26	4.3	0.795	1.9	74.5	7.4	3.5	12.7
P. I, 8 mos., 165 b. p.; edema; general condition fair	32	11	5.0	0.383	24.3	49.3	6.0	2.5	17.9

mum observed either by K. W. Wilson[19] or ourselves in normal pregnancy. The results confirm those obtained by Murlin and Baily with the formol method.

Not a single one of the 10 eclamptic women whose blood was examined for amino nitrogen showed a figure outside the range

TABLE III.—PLASMA BICARBONATE AND NITROGEN DISTRIBUTION OF URINE IN ECLAMPSIA.

History. Para, months pregnant, b. p., etc.	Urine. Total N. g. per 100 c.c.	Urine. Per cent. of total N. as: Albumin.	Urea.	Ammonia.	Total amino-acids.	Undetermined.	C.c. of CO_2 bound by 100 c.c. of plasma. Mother's blood.	Infant's blood.
P. I, 9 mos., 168 b. p.; convulsions	0.554	15.3	57.3	8.1	..	..	52	
P. I, 9 mos., 186 b. p.; blood and urine 48 hours p. p.; coma	1.595	..	..	..	2.6	..	54	
P. II, 24 hrs. p. p., 170 b. p.; eight convulsions; p. p. eclampsia	0.706	1.6	68.5	8.9	2.6	18.4	47	
P. III, 10 hrs. p. p.; 170 b. p.; p. p. eclampsia	0.530	29.2	..	7.9	1.6	..	46	
P. I, 8 mos., 186 b. p.; semicomatose; convulsions; blood 14 hrs. p. p.; urine 30 hrs. p. p.	1.090	3.2	65.7	7.4	2.5	21.2	45	
P. III, 7 mos., 220 b. p.; convulsions and edema	1.025	54.7	27.2	8.3	4.1	5.7	45	
P. VI, 9 mos., 160 b. p.; convulsions; blood and urine 2 days p. p.	0.449	+	75.9	4.5	2.2	17.4	58	
P. I, 8 mos.; convulsions; coma	0.639	Trace	63.3	11.3	4.6	20.8	43	47
P. III, 5 days p. p., 168 b. p.; p. p. eclampsia and convulsions	0.674	25.5	53.1	2.0	2.9	16.5	51	
P. I, 9 mos., 216 b. p.; no convulsions; first specimen one day before delivery; second labor day	0.215	+	56.8	6.0	..	..	47 41	32
P. I, 5 mos., 190 b. p.; preëclamptic	..	..	..	..	..	..	54	
P. —, 9 mos., 156 b. p.; semicomatose; convulsions	..	..	..	..	..	..	45	47
P. I, no convulsions; edema	..	..	..	..	..	..	47	45
P. I, 8 mos., 156 b. p.; coma	..	..	..	..	..	..	44	

TABLE IV.—PLASMA BICARBONATE AND NITROGEN DISTRIBUTION OF URINE IN PERNICIOUS VOMITING.

History. Para, months pregnant, b. p., etc.	Urine. Total N. g. per 100 c.c.	Urine. Per cent. of total N. as: Albumin.	Urea.	Ammonia.	Total amino-acids.	Undetermined.	C.c. of CO_2 bound by 100 c.c. of plasma. Mother's blood.
P. I, 3 mos., 140 b. p.; vomiting two weeks; much emaciated	0.782	1.5	54.8	24.9	2.4	16.4	
P. II, 3 mos.; vomiting one week	1.020	..	46.3	31.2	2.3	..	62
3 months	0.602	..	55.4	27.4	2.3	14.9	
2½ months	1.645	..	67.4	17.5	2.2	12.9	52
3 months	1.791	..	64.1	16.9			
P. II, 2½ mos.; vomiting four weeks; condition bad	0.928	Trace	51.1	29.0	2.9	17.0	41

[19] Johns Hopkins Hosp. Bull., 1916, xxvii, 121.

4 to 8 mg. per 100 c.c. noted by Ellis, Cullen and Van Slyke[20] in a series of normal men. In brief, neither blood nor urine of eclamptic women shows, as a rule, an amino-acid content above normal limits.

Inspection of the other nitrogen figures of the urine shows that the *urea in eclampsia* is usually below the average normal, often strikingly so, even if calculated on the basis of total nitrogen of the urine minus the albumin nitrogen. The only eclamptic urines which showed more than 70 per cent. of urea nitrogen were those obtained one or more days postpartum. The ammonia was often higher than the average in normal individuals, but the abnormality is less striking than that of the urea. The ammonia and urea ratios are suggestive of those which Nencki and Pavlov[21] obtained from dogs from which the livers had been removed.

All the cases of *pernicious vomiting* showed strikingly *high ammonia* percentages. It appears quite possible that this fact may be due, as pointed out by Underhill and Rand,[22] merely to fasting, and that Williams'[23] separation of pernicious vomiting cases into those of toxic and nervous origin, according as the urinary ammonia is high or low, is not justified. Regardless of its etiological significance, however, the frequency of the appearance of high ammonia in pernicious vomiting (none of our 6 cases showed less than 16.9 per cent.) must be admitted to give to the ammonia ratio an undoubted diagnostic value.

The above findings concerning the ammonia and urea ratios in eclampsia and pernicious vomiting confirm the results of Ewing and Wolf.[24]

In our 5 cases of non-toxic pregnancy the nitrogen ratios were normal.

Conclusions.—The toxemias of pregnancy can be attributed neither to failure in diaminization of the amino-acids, nor to the moderate degree of acidosis observed. The nature of the toxin or toxins therefore remains unknown.

The nature of the functional disturbances which cause the abnormal nitrogen metabolism observed also still awaits a satisfactorily conclusive explanation. Nevertheless the constancy of the low urea ratios in the urine in eclampsia, and of high ammonia in pernicious vomiting, lends decided support to the opinion of Ewing and Wolf, that the nitrogen distribution of the urine, considered "in connection with all the data in the case," should assist in diagnosing the toxemias of pregnancy, and in differentiating them from conditions such as nephritis and transitory gastric disorders.

[20] Jour. Am. Med. Assn., 1915, lxiv, 126.
[21] Arch. f. exper. Path. u. Pharmakol., 1897, xxxviii, 215.
[22] Arch. Int. Med., 1910, v, 61.
[23] Johns Hopkins Hosp. Bull., 1906, xvii, 71.
[24] Loc. cit.

A NEW METHOD FOR DETERMINING THE INTRAGASTRIC TEMPERATURE IN MAN, WITH SOME OBSERVATIONS ON ITS VARIATIONS AFTER INGESTION OF HOT AND COLD LIQUIDS AND DURING DIGESTION.

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and
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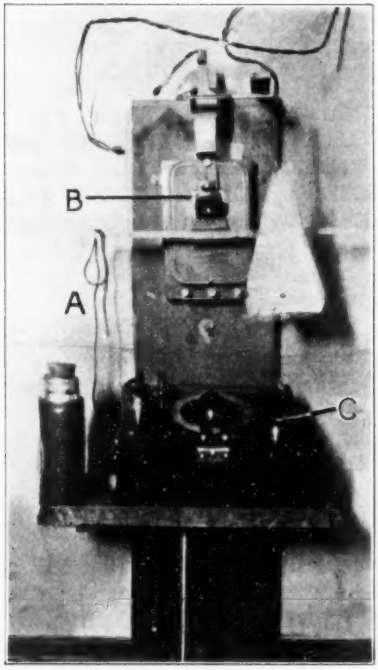
In the Fall of 1914 our attention was attracted to an instrument used by Dr. E. F. Phillips, of the Department of Agriculture, who at the time was investigating the temperature of bee-hives in the Zoölogical Department of the University. This instrument seemed to be especially adaptable to the study of the temperature of internal organs, and consequently we applied it during the next few months to the study of intragastric temperature.

The objects of the experiments we have undertaken were to determine the temperature in the stomach of man during the process of digestion; to test the effects of hot and cold meals; and by comparing the temperature in different parts of the stomach after successive introductions of food and water of varying temperature, to test the correctness of certain views based upon animal experiments regarding the segregation of the stomach contents when separate meals have been taken. In the course of our studies certain other facts came out which may have practical importance.

Previous investigators who have undertaken studies of intragastric temperature seem to have been interested mainly in determining the effect of external applications of heat or cold upon the temperature inside the stomach. Various instruments were employed in these investigations, but most of them were quite crude and did not permit of the determination of rapid changes in the temperature.

D'Hercourt, Chelmonski, Binz, Esmarch, and Schlikoff utilized the mercury thermometer in various forms.

Ewald, the pioneer investigator of stomach temperature, taking advantage of the peculiar ability of a sword swallower, introduced into his stomach a hollow metal tube, through which was inserted a long mercury thermometer, the readings being taken from the protruding end of the instrument. Next he used the Weiderman compass, consisting of a galvanometer and needle, the thermo-element being introduced through a stomach tube. A later and more accurate instrument, that used by Eichler and Schemel, was a resistance thermometer and a registering apparatus consisting of a Deprez d'Arsonval measuring system with a spool and steel magnet. Here also the thermo-element was introduced through a stomach tube.



Photographs illustrating the authors' instrument used in estimating intragastric temperature: *A*, Einhorn duodenal tube containing the thermocouple; *B*, mirror galvanometer; *C*, potentiometer.

The disadvantages of the earlier methods are manifest. The observations were often interrupted and transient; retching and vomiting were frequently provoked by the large size of the instrument introduced, and there was no arrangement by which a meal could be taken with the instrument in position. Thus the satisfactory observation of temperature before, during, and after the introduction of food could not be made.

The apparatus employed in our studies consists of a thermocouple of copper and constantin wires, one pair of ends being placed in a thermos bottle at 0° C. and the other pair being soldered together and run through an Einhorn duodenal tube, at the end of which they were made secure by soldering within the small perforated metal bulb. The thermocouple was then joined to a mirror galvanometer and a potentiometer, the readings being taken in microvolts. This instrument was so calibrated that 40 microvolts corresponded to 1° C., with slight variations at the ends of the scale. Readings could thus be taken within $\frac{1}{40}$° C.

The small caliber of the tubing and of the bulb, which is scarcely larger than a 5-grain capsule, facilitated the ready introduction of the bulb into the stomach and eliminated the tendency to retching and vomiting. The fact that full meals could be taken alongside the tube and that the fluoroscope could be used in locating the position of the metal bulb, thus enabling one to observe variations in temperature between pyloric and fundic areas, are sufficient indications of the advantages of this method.

Comparison of Temperature at the Fundus and Pylorus after Ingestion of Cold Liquid. The bulb was first inserted into the fundus and then into the pylorus of the normal empty stomach and the constant temperature of these regions determined. Next, the bulb being placed in the fundus, the patient was given 120 c.c. of ice water and the temperature recorded; then more of the tube was swallowed, permitting the bulb to work over to the pyloric region, in which portion readings were again taken. Every few minutes, by withdrawing or advancing the bulb, readings were taken at these two areas. The fluoroscope was used in locating the position of the bulb. A short series of practically normal cases revealed the facts shown in the accompanying table:

Showing Comparison of Temperature in the Fundus and the Pyloric Portion of the Stomach after Ingestion of Cold Liquid.

Case.	Temperature before water taken.		Ice-water.	Drop in temperature.		Time to return to normal.
	Fundus.	Pylorus.		Fundus.	Pylorus.	
1.	38.0° C.	38.0° C.	120 c.c.	14.2° C.	8.9° C.	20
2.	37.9° C.	37.9° C.	120 c.c.	6.4° C.	5.1° C.	19
3.	37.9° C.	37.0° C.	120 c.c.	8.1° C.	1.2° C.	30
4.	36.9° C.	36.9° C.	120 c.c.	5.2° C.	1.0° C.	31
5.	36.9° C	36.9° C.	120 c.c.	12.8° C.	8.7° C.	24

1. The prolonged time required for the return to normal temperature, considering the small amount of liquid taken.

2. The marked drop in temperature at the fundus.

3. The striking difference in fundic and pyloric regions. The great difference in temperature of fundus and pylorus after the introduction of cold drinks or ice-cream, as well as the length of time required for the stomach to resume normal temperature, are of special interest in that they confirm, from a different stand-point, the comparatively recent researches of Grützner, Cannon and others.

Physiologists of today consider the fundus a reservoir for retaining the bulk of the food, the more muscular pyloric region being the active motor area. They believe that the material may remain in the fundic region undisturbed for a long time and thus escape mixture with the acid gastric juice, so far, at least, as the interior of the mass is concerned. Grützner after feeding rats differently colored foods and then making sections of the stomachs found that successive portions were arranged in definite strata. Food first taken lay against the walls, while succeeding portions were arranged regularly in the interior in concentric fashion.

Our observations tend to confirm these views, and at least disprove conclusively the old conception that the contents of the stomach are kept in a constant general rotary movement.

Tests Showing the Influence of Hot and Cold Foods upon the Intragastric Temperature. The instrument being in place, a meal consisting of 360 c.c. of ice water with two slices of bread was given to a normal case. At intervals throughout the observation the position of the bulb was alternated between the fundus and pylorus. The greatest drop, *i. e.*, 8.5° C., occurred in the fundic portion, and no less than forty minutes were required for the return to normal temperature at that area. At the pyloric area there was a fall of 4.1° C., which returned to normal somewhat more promptly. Cold milk instead of cold water produced approximately the same results.

Large meals with hot and moderately cold foods mixed showed slight transient fluctuations with the bulb alternating between fundus and pylorus; but when at the end of the meal ice-cream was taken there was a drop of 7.9° C. at the fundus and 3.3° C. at the pylorus, and forty-five minutes were required for the resumption of normal temperature, which occurred at both areas at nearly the same time. When hot coffee was taken after the ice-cream an immediate return to normal temperature was observed.

The accompanying chart illustrates the fluctuations occurring in one instance after the ingestion, in turn, of hot coffee, a full meal, and then after an interval of twenty minutes a glass of ice water. After the water, frequent readings were taken over a period of forty minutes until both fundic and pyloric temperatures had returned to normal. Then after a further period of twenty minutes a moderate

amount of ice-cream was taken, with a resulting pronounced and prolonged fall in the fundic region accompanied by a less marked and shorter drop in the pyloric area.

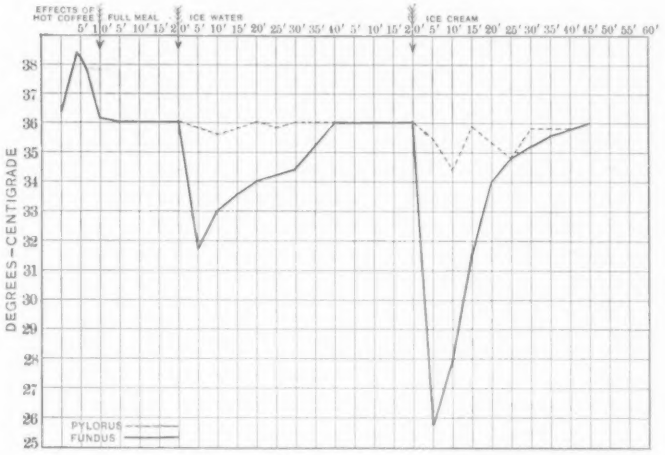


Chart illustrating the effects of food of varying temperature upon the fundus and pyloric portion of the stomach.

Pyloric Temperature. In observations on the pyloric temperature alone the bulb was introduced into that region and left undisturbed. The bulb was located by the fluoroscope and was found well within the pyloric part of the stomach. An ordinary meal was then given and no change of temperature noted. The taking of ice water just after the meal caused a drop of but 1.2° C. at the pylorus in the course of the next thirty-five minutes.

Observations during Digestion after Elimination of Food Temperature Variations. Next a series of cases was studied with the idea of observing slight changes during digestion, eliminating fluctuations due to the temperature of the test-meal. The bulb having been introduced into the fundus, the patient was given 360 c.c. of milk and two slices of bread heated to body temperature. Oral and rectal controls were taken at frequent intervals. No changes were demonstrable in the intragastric temperature during a period of over one hour in any of the cases observed.

Tests in Abnormal Stomachs. In a few cases of hyperacidity and hypermotility, readings of the temperature were made before and during the gastric digestion to determine if any variations occurred, but the results were negative. One case of this type in which a neurotic element was very marked, and in which there was a great increase in motility, showed no difference in temperature

of fundus from that of pylorus when ice water was taken on an empty stomach.

There was a drop of 5° C. at both areas; the return to normal required twenty-six minutes. Belching and retching continued irregularly throughout the observation, and doubtless aided in the premature mixing of the gastric contents.

Effects of Local Applications. Ice-bags applied over the gastric area produced an average drop of 0.9° to 1° C. in the course of forty-five minutes, while the effects of hot-water bottles applied in the same position were very slight—in fact, almost negligible during three-quarters of an hour.

As has been said, the effects of local applications of heat and cold were the special subject of investigation by former experimenters in this field, and for that reason but few tests were made by us. Our findings confirm those of Chelmonski, Wendrimer and Schutze, Eichler and Schemel[1] and others, who conclude that cold applications to the body surface cause a lowering in temperature of the underlying organs and warm applications affect temperature to a less degree.

We detail only the results of our observations without making any practical deductions at this time. It is obvious that hot and cold foods taken alternately may influence the functions of digestion favorably or otherwise. Extended observation with the aid of the method here used seems to us highly desirable.

AN ASPIRATING BOUGIE FOR THE ESOPHAGUS AND STOMACH.[1]

By Max Einhorn, M.D.,

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In examining patients with digestive disturbances we are occasionally uncertain as to the choice of instrument for the first examination. Generally the stomach tube is used, excepting when we suspect an obstruction along the esophagus. In the latter instance a bougie with an olive-shaped end is employed. Should we find that there is no stenosis, then a second examination with the stomach tube becomes necessary. Even in encountering a resistance with the bougie, it is often desirable to ascertain whether there is fluid or mucus or decomposed tissue in the vicinity of the affected area. To decide this another examination with the stomach tube must be

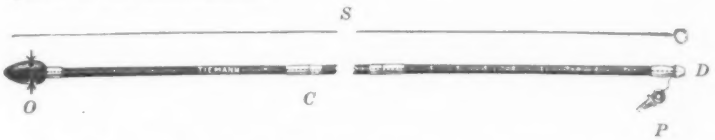
[1] Deutsch. med. Wchnschr., 1911, No. 51.

[1] Demonstrated at the New York Academy of Medicine (Section on Medicine), March 21, 1916.

undertaken. The class of cases under consideration are often in a weakened condition, and any instrumental manipulation on them, even if done with the greatest of care, causes some discomfort.

It appeared to me, therefore, of advantage to construct an instrument which could be used for both purposes at the same time, namely, for the detection of strictures and also for obtaining fluids. The following is a description of the bougie:

The aspirating bougie resembles the usual whale-bone bougie, with the difference that the whale-bone is replaced by a canal-bearing catheter (size 14 F. twenty-four inches long), and that the olives are hollow and perforated in such a manner that fluids can easily be aspirated by a syringe. Different sized olives can be screwed on. The stem is divisible and screwed together in order to be easily handled. A wire stylet or mandrin serves to give the stem the requisite stiffness. A plug is fastened on the distal end. Before withdrawing the instrument the plug is inserted into the distal opening in order to retain any material within the olive for inspection and examination. The drawing illustrates the different parts of the instrument.



The aspirating bougie for esophagus and stomach. *O*, perforated olives of various sizes; *C*, catheter, 14 mm. in circumference and 60 cm. long; *D*, distal end; *P*, plug, attached by thread; *S*, wire stylet.

The same instrument can also be used for obtaining gastric contents in patients who cannot swallow the usual stomach tube, as it can be easily introduced without much assistance on the part of the patient. It can also be employed for fractional tests if desired.

I have used the aspirating bougie, made for me by Messrs. Tiemann & Co., with great satisfaction, and I herewith recommend it to the profession.

THE TREATMENT OF CIRCULATORY FAILURE IN ACUTE INFECTIONS.[1]

By Malcolm Goodridge, M.D.,

Assistant Professor of Therapeutics, Cornell University Medical College, New York City.

Before we can intelligently combat the symptoms which arise in the course of acute infectious diseases connoting failure of the

[1] Read before the Hospital Graduates' Club, December 23, 1915.

circulation, it is obvious that we should have some understanding of the factors involved in such failure, and if a careful examination of the evidence derived from the experimental laboratory and from the bedside of our patients does not permit us to draw definite conclusions as to what portion of the circulatory mechanism is at fault when such symptoms present themselves, we should at least be prepared to apply our therapeutic efforts in such emergencies with rational empiricism.

In 1899 Romberg and Pässler,[2] in a series of experiments on animals, apparently demonstrated that the collapse observed in various acute infectious diseases was due to paralysis of the vasomotor center in the medulla. They based their belief on their failure to obtain any rise in blood-pressure in asphyxia occurring in pneumonia, diphtheria, septicemia, and other infections after stimulation of the nasal mucous membranes or on stimulation of the central end of the sciatic nerve.

So generally was this work of Romberg and his associates accepted and applied to the human subject suffering from an apparently similar condition, that one will find in nearly all modern theses on the treatment of circulatory failure in acute infections the statement that treatment should be aimed at the vasomotor centers rather than at the heart.

The impulse which served to start the pendulum on its swing away from Romberg's teaching was initiated by Porter[3] and his assistants. They injected animals with a lethal dose of diphtheria toxin, and then, several hours before death would probably have taken place, determined, by the average time of death in control animals, the state of the vasomotor center was tested by measuring the reflex change in blood-pressure obtained by stimulating the depressor and sciatic nerves. Stimulation of the central end of the depressor nerve caused a fall in blood-pressure averaging 36 per cent. of the blood-pressure before such stimulation, while the average rise in blood-pressure obtained after sciatic stimulation was 33 per cent., and they concluded that "the experimental evidence proves that the vasomotor center is not impaired in fatal diphtheria intoxication."

Porter and Newburgh[4] in a series of experiments on animals undertaken to ascertain the state of the vasomotor apparatus in pneumonia, demonstrated "a normal vasomotor reflex with almost wholly consolidated lungs in animals about to die," and they concluded that "experimental evidence proves that the vasomotor center is not impaired in fatal pneumonia."

Romberg and Pässler in their experiments on animals produced fatal pneumonia and diphtheria, and when the animal was near death they massaged the abdomen and caused by this procedure a

[2] Deutsch. Arch. klin. Med., 1899, lxiv, 652.
[3] Am. Jour. Physiol., xxxiii, 431. [4] Ibid., xxxv, 1.

moderate rise in blood-pressure, and they argued that if the heart muscle was exhausted it would yield to this increase in load and no rise in blood-pressure would follow. That such a conclusion was not justified was shown later by several observers, who proved that massage of the splanchnic area would cause a rise in arterial pressure even in dead animals.

MacCallum[5] injected dogs with diphtheria toxin and found that "though the hearts from poisoned animals are rather weak and apt to be irregular, it is clear that they continue to beat for several hours after they have shown every sign of failure in the body of the dying animal if only the pressure of nutritive fluid be maintained in the coronary arteries . . . all of this seems to show fairly well that the death which occurs in the height of an attack of diphtheria is not exclusively the result of direct injury to the heart, although that may play some part in the process."

Porter and Newburg[6] demonstrated that the heart muscle of a dog which has died of pneumonia contracts as well as the heart muscle from a normal dog, provided the vessel to this muscle is fed with normal blood. They observed that pneumonia blood suddenly fed to a normal heart muscle lowers its efficiency, but that heart muscle gradually exposed to the poison adjusts itself to its poisoned food, and as a result of their experiments they conclude that the heart muscle is not functionally impaired in pneumonia. Clinical observation on the blood-pressure in pneumonia rather supports the experimental evidence produced by Porter that failure of the vasomotor center is at least not always the cause of death in cases which terminate fatally with symptoms of circulatory collapse.

Gibson formulated a rule based upon the pulse-rate and blood-pressure readings in pneumonia which he considered of important prognostic significance in this disease. The rule is that "when the blood-pressure expressed in millimeters of mercury falls below the pulse rate per minute expressed in figures the prognosis is unfavorable."

Newburgh and Minot,[7] however, have demonstrated the fact that the systolic pressure readings in some fatal cases of pneumonia tend to be higher than in those which recover, and in applying Gibson's rule, found that the rule obtained in but 43 per cent. of the cases observed, and they concluded that:

1. The blood-pressure curve does not suggest failure of the vasomotor center in pneumonia.
2. Low systolic pressures are not invariably of evil omen.
3. Blood-pressure measurements cannot be used as a basis for treatment.

There is nothing to justify the assumption that the heart is entirely at fault in the presence of symptoms of circulatory failure

[5] Am. Jour. Med. Sc., cxlvii, 37.
[6] Jour. Exp. Med., xxii, 123.
[7] Arch. Int. Med., xiv, 48.

occurring in the course of acute infections, nor, on the other hand, is there sufficient clinical or positive experimental evidence to permit one to exclude the heart as a factor at least in such failure.

The symptoms which we have been in the habit of ascribing to failure of some portion of the circulatory mechanism in human beings suffering from acute infectious diseases are, briefly: cyanosis; dyspnea; a rapid pulse, rapid out of proportion to the height of the fever; or a pulse-rate which is increasing while the temperature is falling; a sudden fall in blood-pressure; increase in the area of cardiac dullness, especially to the right; a failing first sound at the apex or a diminution in the intensity of the second sound over the pulmonary area; cardiac irregularities; and pulmonary edema.

It has been generally believed that the circulation in the body is maintained chiefly by two factors: the force of the heart as a pump and the peripheral resistance in the vessels maintained by the contraction of the small arteries, which in turn are in a measure controlled by an active vasomotor center in the medulla; but in the light of our present knowledge concerning the integrity of the vasomotor centers in acute infections and in the absence of positive proof that the myocardial efficiency is impaired in such conditions, it seems possible at least that there is a *tertium quid*, a third something, operating outside the heart and vasomotor centers, though more or less intimately associated with them, which controls the flow of blood.

The balance between the circulation and respiration is maintained by conditions existing in the blood. The action of the blood on the respiratory mechanism is not due to CO_2 alone, but also to the presence in the blood of non-volatile acids; and it does not seem probable that one part of the respiratory mechanism, the ventilation of the lungs, is delicately balanced, while the other mechanism, the circulation of the blood, is not so balanced; and Boothby suggests that the factor which regulates respiration and governs the ventilation of the lungs also governs the circulation of the blood.[8] Porter has recently questioned the generally accepted theory that both the vasomotor reflexes and the arterial tonus are controlled by the same center, the vasomotor center, and suggests the possibility of the existence of a vasotonic and vasoreflex center related but separable.[9] Boothby's work suggests the possibility of a combination of a subordinate circulatory center and a ventilation center.

In the rational treatment of a pathological process we must recognize not only the necessity for intelligent management of complications which may arise in the course of such a process, but we must also have a keen appreciation of those procedures which may be instituted in order that such complications may be antici-

[8] Jour. Am. Med. Assn., lxv, 959. [9] Ibid., lxiv, 1659.

pated and possibly prevented. So in a discussion of the treatment of circulatory failure it is necessary to emphasize those factors which are unfavorable to the maintenance of good circulation.

The importance of rest to the patient is perfectly obvious. In the management of any diseased condition, modern therapeutic effort seeks to spare bodily function, and rest in acute infections means circulatory prophylaxis in its very broadest sense. So we select for our patient a comfortable bed that he may obtain the greatest degree of muscular relaxation. We endeavor to relieve his cyanosis, dyspnea, and nervous manifestations by giving him fresh, circulating, and, if possible, cold air. We seek to relieve, by appropriate measures, excessive or unproductive cough, to combat tympanites when it occurs, to relieve excessive pain, and to promote quiet and restful sleep by every means possible. Careful attention to such details constitutes a very important part of the effort we should make to conserve the efficiency of the entire circulatory mechanism.

Tradition must play no part in dictating to our therapeutic judgment in the selection of various drugs by means of which we endeavor to combat the symptoms of circulatory failure when they have occurred, and I say this with a very full appreciation of the necessity for empiricism even in present-day treatment. The drugs which I have chosen to discuss are: alcohol, strychnin, camphor, epinephrin, pituitary extract, the nitrites, and digitalis.

Alcohol. Delafield in his lectures on pneumonia and diphtheria says: "The heart failure is of the same character that we get in any of the severe infectious diseases." . . . "It requires the ordinary management with alcohol and cardiac stimulants."

Janeway[10] says: "Least of all of the so-called stimulants does alcohol deserve the name. It is without influence on blood-pressure or the force of the heart in animals, normal men or diseased conditions."

And these two statements admirably represent the difference, as far as this drug is concerned, between the therapy of twenty years ago and the present-day therapy.

I am loath to discard any of the teachings of that master mind in medicine, Dr. Delafield, for he was a keen observer, and most of the statements made by him years ago hold good for today; but alcohol today is not considered to stimulate any portion of the cardiovascular system—indeed, there is much evidence that it does just the contrary. I am speaking of alcohol now purely from the stand-point of its effect on the circulation. It may do good in relieving active delirium; in fact, I believe that it does; but it is of value here because of its depressant effect on the higher centers already overstimulated by the toxemia of the disease and not

[10] Clinical Study of Blood-pressure, 223.

because it stimulates the circulation. Alcohol causes dilatation of the skin vessels after moderate doses. Large doses cause a fall in blood-pressure; the heart-rate is not changed by therapeutic doses.

Lieb[11] in an effort to determine the reflex effects of alcohol on the circulation found that moderately strong alcohol taken by the mouth produces local irritation of the gastric mucous membrane. Such irritation produces a rise in blood-pressure and an accelerated heart; but if alcohol is given well diluted by the mouth it causes no local irritation, and there is, in consequence, no rise in blood-pressure. Lieb gave cats doses of alcohol varying from 0.5 c.c. to 5 c.c., and in no case was there any change in heart-rate or blood-pressure within half an hour of its administration. He made forty-three observations on twenty-one different patients suffering from various acute infections, typhoid, pneumonia, rheumatism, malaria, etc.

In one patient alcohol was given at a time when circulatory stimulation was called for, yet alcohol not only did not produce any improvement, but, on the contrary, it actually decreased the efficiency of the circulation.

Lieb believes that in the presence of severe toxemia, alcohol loses its power to raise blood-pressure even reflexly. He says: "Advocates of the use of alcohol may claim that alcohol improves the circulation in some fashion other than raising blood-pressure or increasing the heart-rate." It may increase the velocity of the flow or it may improve the efficiency of the heart as a pump; but in applying Tigerstedt's formual $1 \frac{PP \times PR}{SP \times PR'}$ Lieb showed that the changes induced by alcohol in these factors was very slight; in fact, the efficiency of the heart as a pump was decreased.

His conclusions with his experiments as a basis were that "Even though alcohol may raise for a few moments the systolic blood-pressure, and thus act as an apparent circulatory stimulant, it cannot be regarded as a true circulatory stimulant, inasmuch as it decreases cardiac efficiency, raises disproportionately the diastolic-pressure, and lowers pulse-pressure." And in my opinion this statement just about represents the value of alcohol as a cardio-vascular stimulant.

STRYCHNIN is another drug which enjoys a considerable reputation as a circulatory stimulant. Tradition and tradition alone is responsible for its use as such. Vague expressions as to its clinical value, estimated by the feel of the pulse, the subjective improvement of the patient, are frequent in medical literature in this country and to some degree in England. Little is seen in the German and French literature of its use for this purpose. It has never been shown that strychnin does or can relieve cardiac failure. As keen

[11] Jour. Am. Med. Assn., lxiv, 898.

an observer as Mackenzie says of it: "I have carefully sought for its special effect on the heart and found none."

Newburgh[12] in his experiments on patients with this drug shows that "none of the patients were benefited by strychnin; compensation was not improved in the slightest," and he concludes that "neither pharmacological nor clinical evidence justifies the use of strychnin in the treatment of acute or chronic heart failure."

Pilcher and Sollmann[13] show that therapeutic doses of strychnin have no direct effect on the heart. There is no action on the blood-vessels directly. It produces no marked or constant effect on blood-pressure, and they conclude that doses of strychnin large enough to be dangerous (0.05 mg. per kilo) are "usually without action on the vasomotor center, but may stimulate the center moderately."

Parkinson and Rowlands,[14] in England, found no evidence that strychnin used subcutaneously in full doses in cases of cardiac failure produced any change in blood, the blood-pressure, rate of pulse, rate of respiration, or general symptoms within an hour after administration, and concluded that strychnin has no effect which justifies its employment as a cardiac stimulant.

Newburgh[15] showed that strychnin sulphate in medicinal dosage does not increase the output of the heart.

It is, of course, true that the empiric use of drugs is occasionally beneficial; but here is a drug which has been praised as a cardiac stimulant by some observers that fails absolutely to produce results in cardiac failure, and in cases too that responded, after its use, immediately to digitalis in the ordinary manner.

With such weight of evidence against its value, surely we must admit that it is at least a very slender reed to tie to in case of such dire need as often presents itself in the circulatory failure of such diseases as we are discussing.

Camphor has more to recommend it in the circulatory failure of the acute infectious diseases than either alcohol or strychnin, but since I have said that these two drugs are absolutely valueless, I fear that my statement with reference to camphor condemns it with faint praise. Edsall and Means[16] in a series of experiments carried out in human beings to determine the effect of various drugs on the respiration and respiratory metabolism, concluded that "the results obtained with camphor show no constant effect. In one experiment there was a slight fall in CO_2 tension, suggesting that there may have been some stimulation of the center, but in the other experiments there was none. Circulation rate and respiration rate are essentially unaltered."

[12] Am. Jour. Med. Sc., cxlix, 696.
[13] Jour. Pharmacol. and Exp. Ther., vi, 331.
[14] Quart. Jour. Med., vii, 42.
[15] Arch. Int. Med., xv, 458.
[16] Ibid., xiv, 897.

Heard and Brooks[17] in clinical experiments with camphor injected subcutaneously in oil in doses up to 50 grains failed to produce any definite effect.

Plant[18] in his experiments with the effects of camphor on the normal isolated dogs' heart muscle failed to produce any distinct and constant stimulation.

Pilcher and Sollmann[19] in their experimental work with the effects of drugs on the vasomotor center concluded as to camphor that in therapeutic doses it is probably without action on this center.

I am perfectly willing to admit that the centers may be more easily influenced when depressed by disease than when in the normal state.

I have used camphor as a stimulant in acute fevers with symptoms of circulatory failure, and I have thought that it did good, but there are other drugs of much more certain practical and theoretical value.

EPINEPHRIN is fleeting in its action, and in consequence should not be prescribed when sustained effect on the circulatory mechanism is desired. Epinephrin when injected intravenously or intermuscularly causes a prompt rise in blood-pressure, due to the direct action of the drug on the muscles of the vessel wall or on the terminations of the nerves in them.

The heart is at first accelerated and then slowed, the acceleration being due to stimulation of the accelerator fibers in the heart muscle, and the heart, in consequence, contracts more strongly and more completely.

The slowing of the heart is a vagal effect, not direct, but incidental and subsequent to heightened blood-pressure. It has no direct effect on the vasomotor apparatus, but frequently there may be slight stimulation of this center, secondary to the rise in blood-pressure.

Experimental evidence produced by Barbour and Prince[20] shows that epinephrin has the same effect on the coronary vessels of the heart in man as the members of the digitalis group, excepting digitonin—that is, it causes constriction of these vessels.

Epinephrin is, therefore, indicated when there is evidence of acute circulatory collapse with falling blood-pressure and rapid pulse. Janeway,[21] in an article on "The Comparative Value of Cardiac Remedies," says: "I have seen the most amazing restoration from apparent imminent death follow the intravenous injection of epinephrin in large doses; in one case over 4 c.c. of 1 to 1000 solution in a little more than one hour. This was in a case of pneumonia with extreme cyanosis. Life was prolonged for three days."

There is every evidence, experimental and clinical, to warrant

[17] AM. JOUR. MED. SC., cxlv, 238.
[18] Jour. Pharm. and Exp. Ther., v, 571.
[19] Ibid., vi, 345.
[20] Jour. Exp. Med., xxi, 330.
[21] Loc. cit.

the use of epinephrin in acute circulatory collapse occurring during the course of such an acute infection as pneumonia. Indeed, in spite of its fleeting action, one may tide his patient over a circulatory crisis and actually save life by its use.

A word of caution is necessary concerning the age of the preparation of epinephrin to be used. Apparently a product which has been exposed for some time loses its constrictor effect, but not its dilator, and a fall in pressure instead of a rise may take place after the intramuscular or intravenous use of such a preparation.[22]

PITUITARY EXTRACT of the infundibular portion of the pituitary gland has an action very similar to that of epinephrin, the difference between the two being rather a matter of intensity than of kind. Blood-pressure is raised, but not so rapidly nor so high as after adrenalin; but the effect lasts for a much longer time. The blood-pressure is raised by direct action on the bloodvessels. Pilcher and Sollmann[23] demonstrated that in animals it had no effect on the vasomotor centers.

The indications for its use are the same as those enumerated under adrenalin, with the addition possibly of its value in the treatment of tympanites when by stimulating the paretic intestinal muscles it often relieves distention, and in consequence the heart is relieved of an important mechanical element favoring failure of the circulation.

THE NITRITES, *i. e.*, nitroglycerin, amyl nitrite, and sodium nitrite, have a distinct place in the therapeutic armamentarium of the physician called upon to treat one type at least of cardiovascular failure occasionally seen in acute infections, more often perhaps in lobar pneumonia than in other infections, namely, pulmonary edema.

The nitrites cause direct peripheral depression of the arterioles, with a consequent fall in pressure. The vasomotor center is never depressed in animals by the use of the nitrites. In fact, Pilcher and Sollmann[24] proved that stimulation was the rule. Such stimulation probably is due to the anemia of the centers caused by the dilatation of the peripheral vessels.

Another important observation made by Macht[25] is the effect of the members of this group on excised strips of medium-sized pulmonary arteries. The nitrites caused constriction of the pulmonary strip. This action of the nitrites is corroborated by other experimental data, and the explanation of such action is that the pulmonary artery is richly supplied for the most part with vasoconstrictor nerve terminals. It is this selective action of the nitrite group of drugs which makes them valuable in the treatment of some cases of pulmonary edema.

[22] Jour. Am. Med. Assn., lxiv, 1396.
[23] Jour. Pharm. and Exp. Ther., vi, 405.
[24] Ibid., vi, 323.
[25] Ibid., vi, 13.

CAFFEIN. The effects of caffein on the circulation have been studied both pharmacologically and clinically by several workers during the past two years. Pilcher and Sollmann[26] found in experiments conducted upon animals that caffein caused vasodilatation with sufficient cardiac stimulation to maintain or even somewhat increase blood-pressure.

These actions favor flow, and I shall refer presently to work done by Means and Newburgh to show that it does increase the flow of blood in human beings. This is certainly a highly desirable effect in circulatory disturbance.

Pilcher and Sollmann conclude, as a result of their experiments on animals, that caffein causes: (1) cardiac stimulation; (2) increase in heart rate which is not due to vagus depression; (3) vasodilatation through peripheral depression of the vasoconstrictor mechanism; (4) central vasoconstrictor stimulation is generally ineffectual.

The acceleration in the heart-rate is probably due to direct action of the drug on the heart muscle.

While Edsall and Means,[27] Lucas,[28] and later Newburgh[29] noted little or no effect on blood-pressure, or on the rate or character of the pulse, from caffein administered in therapeutic doses to patients suffering from acute infectious diseases with or without low blood-pressure, Means[30] and Newburgh report an extremely interesting and important series of experiments conducted on human beings in order to determine the effects of caffein on the blood-flow in normal human beings. Their method consisted in determining the rate of absorption of nitrous oxide gas in the lungs. Nitrous oxide gas forms no chemical combination with hemoglobin, but goes into physical solution in blood plasma, so according to a definite coefficient it was possible to calculate how much blood must have passed through the lungs in order to absorb a measured amount of nitrous oxide gas from an original mixture of known concentration.

The blood-flow as determined by this method is, of course, that flowing through the lungs or from right to left heart. There is a marked variation in blood-flow during rest, and this is due to the fact that during rest the supply of blood is "inadequate" to fill the ventricles to their utmost capacity during each diastole; under such circumstances the output of the heart is dependent upon the supply of venous blood and is not directly related to the functional capacity of the heart. During work the flow of blood shows less variation; in other words, "during work the supply of blood to the heart becomes adequate." They showed that during rest or when

[26] Jour. Pharm. and Exp. Ther., iii, 89.
[27] Arch. Int. Med., xiv, 897.
[28] Am. Jour. Dis. Child., vii, 208.
[29] Arch. Int. Med., xv, 458.
[30] Jour. Pharm. and Exp. Ther., vii, 449.

the supply of venous blood is "inadequate," caffein frequently causes a rise in total blood-flow, and often this increase occurs without corresponding rise in pulse-rate. During work no action was obtained from caffein other than an increase in pulse-rate, and consequently there was a slight diminution in systolic output. They suggest in conclusion that during rest or when the flow of blood to the right heart is "inadequate," caffein increases the flow by increasing the venous supply through action on some mechanism outside the heart, when the supply becomes "adequate" or approaches adequacy no such action is obtained.

DIGITALIS and the other members of this group of drugs is, according to some observers, of little value in the treatment of circulatory failure occurring in the course of acute infectious diseases.

Mackenzie says that "I have never seen much good follow the administration of digitalis in acute febrile conditions;" and again, "Digitalis will be found to be of little value when the heart is already in the grip of some poison, whether it be the specific organism of such diseases as rheumatism, pneumonia, etc., or the toxins of such diseases or such poisons as alcohol."

Gibson says that "In the worst cases of pneumococcal poisoning the heart refuses to respond to digitalis."

Janeway believes that "Digitalis given by the mouth in these cases is worthless." Krehl, on the other hand, believes it to be beneficial.

Just what is meant by the failure of digitalis to act in the presence of fever is not altogether clear. If a reduction in rate is the action expected in this type of case, one can understand why it is said to be of no value. The most decided effects on rate after digitalis administration are noted either in those cases in which the normal pacemaker is eliminated, as in cases of auricular fibrillation, or in those cases with a normally functioning sinoauricular node in the presence of edema.

In view of the work of Cohn[31] in an electrocardiographic study on the action of digitalis it seems probable that slowing the rate of the heart is not at least a "primary function of digitalis." He showed in individuals with a regular rate that digitalis caused a definite lengthening of the conduction time between auricle and ventricle, and also that it produced a distinct "alteration in the size, shape, and direction of the T-wave in the electrocardiogram. These effects were produced in persons with perfectly normal hearts, and even in the absence of any effect on rate. Precisely the same effects were noted in febrile cases, thus proving that whatever its nature the "same sort of support can be given the heart by digitalis during fever as in its absence."

[31] Jour. Am. Med. Assn., lxv, 1527.

In febrile cases showing abnormal rhythm, such as fibrillation and flutter, precisely the same effects on rate were noted after the administration of strophanthin intramuscularly or digitalis by the mouth as obtain in similar conditions occurring in non-febrile states.

Jamieson[32] as a result of his experiments on animals undertaken for the purpose of ascertaining whether the action of a digitalis body when administered to animals suffering from pneumonia differed in its action when no infection or fever was present, concluded:

1. When a like amount of strophanthin is injected intravenously, the mortality is the same in both normal cats and in cats suffering from induced pneumonia.

2. The presence of an acute infection in these animals does not interfere with the action of strophanthin on the heart.

3. The identity of strophanthin action in infected and normal animals renders it probable that a like similarity may be anticipated in man under normal conditions and in pneumonia.

Gunn[33] in his experimental work conducted in animals to demonstrate the influence of temperature on the action of strophanthin on the mammalian heart, showed at least high fever is not the cause of failure of action of digitalis, and that if the heart does not respond to digitalis bodies, it is probable that the heart is in a refractory state from the presence of toxins.

Sollmann, Mendenhall and Stingel[34] agree in the main with Gunn, for they proved that in animals at least ouabain or crystalline strophanthin acts more quickly on the isolated rabbit's heart as the temperature of the animals is raised.

CONCLUSIONS. 1. There is neither clinical nor experimental evidence to support the belief that failure of the vasomotor center is the cause of the symptoms of circulatory failure which occur in acute infectious disease.

2. While it has been shown experimentally that the heart is not exhausted in animals dying of acute infectious diseases, there is no positive proof that the myocardium is wholly efficient in its effect to maintain the circulation in the body of the living animal under such circumstances.

3. The hypothesis which suggests the existence of a third center controlling the flow of blood is important even though it is not yet proved.

4. Alcohol and strychnin are absolutely worthless drugs in the treatment of circulatory failure.

5. Epinephrin and pituitary extract are useful in the treatment of sudden circulatory collapse, but their action is not a sustained one.

[32] Jour. Exp. Med., xxii, 629.
[33] Jour. Pharm. and Exp. Ther., vi, 39.
[34] Ibid., vi, 533.

6. The nitrites are valuable additions to our therapeutic armamentarium in the treatment of pulmonary edema under certain circumstances, because of their selective action in constricting the pulmonary arteries.

7. Caffein increases the flow of blood when the supply to the heart is "inadequate," probably by an action on some mechanism outside of the heart.

8. One of the most important contributions of recent times on the action of digitalis is the proof electrocardiographically that it exerts precisely the same effect on the heart in febrile conditions that it exercises in non-febrile states, and whether the rhythm is initiated in the normal pacemaker or not.

REVIEWS

A Manual of Hygiene and Sanitation. By Seneca Egbert, A.M., M.D., Professor of Hygiene, Medico-Chirurgical College, Philadelphia. 6th edition. Pp. 525; 146 illustrations. Philadelphia and New York: Lea & Febiger, 1916.

Although primarily a text-book for students, the chapters devoted to disposal of sewage, industrial and occupational diseases, and to military hygiene are of equal interest to the practitioner.

The introduction, Chapters II, III and IV, on bacteriology, atmosphere, and ventilation and heating, contain nothing new, though the common-sense rules as applied to the last named topic may interest doctors who have suffered by the over-heated and under-ventilated hospitals in which we all must serve.

Chapter V on water supply presents nothing of interest save a quotation from Parkes, who places malaria in the group of water-borne diseases, apparently from ingestion, which is questionable, to say the least.

Chapter VI treats of dietetics in the ordinary way. It is interesting to note in a work published in 1916 that lettuce and celery are classed as "nerve sedatives."

The chapter on industrial hygiene is interesting, but too brief. One expression deserves favorable comment, in a time when many rush to the conclusion that all industrial evils are due to employers, not to employees: in brief, it is emphasized that all the ills to which wage-earners are heir cannot fairly be blamed on occupation, but that some consideration must be given to the personal habits of the individuals outside of work hours.

The subject of military hygiene, treated in Chapter XIV, should be of special interest to the many doctors of today who have enrolled in the Medical Reserve Corps, most of whom are totally ignorant of military training and discipline. The comments on volunteers or militia leaving ordinary civil occupations and plunging into totally different surroundings are quite to the point. This applies equally to those who volunteer in the line or in the medical corps. The author's reference to the Spanish War should be remembered, containing a partial quotation from Dr. Victor C. Vaughan's address to the American Medical Association in 1900: "Camp pollution was the greatest sanitary sin in 1898."

A brief chapter on vital statistics emphasizes the ridiculous incongruity of our system, due to the lack of uniformity in our several States.

The reviewer suggests bad politics as a possible etiological factor in both of the last mentioned abuses. A. G.

THE CLINICS OF JOHN B. MURPHY, M.D. Volume V, Nos. 3 and 4. Philadelphia and London: W. B. Saunders Company, 1916.

THE June number of the *Clinics* opens with a short talk by Dr. Coffey, in which he advocates the two-stage operation in certain lesions of the gastro-intestinal tract. A large proportion of the volume is devoted to the surgery of the alimentary system, and contains an unusual amount of information in addition to the operative procedure employed in a group of well-selected cases. There is also a group of gynecological cases presented with critical analyses of the history and symptomalology. The editor supplements the text in several instances by statistical reports from Deaver's clinic.

The August number contains more than thirty cases, embracing a great variety of lesions. It is probable that the editor's care to avoid excessive repetition is responsible for recording some of the rarer cases. The reader will be impressed with the remarkable versatility of a surgeon whose work includes such variety. It is worthy of note that there are many appropriate references to the current literature in the recent numbers, as well as frequent references to similar previously published cases which enhance the value of the volume to one who is particularly interested in Murphy's teaching on certain subjects, as for example, ankylosis of the temporomandibular joint which is a feature of this number.

G. M. L.

THE PHYSIOLOGICAL AND PATHOLOGICAL CHEMISTRY OF METABOLISM. By DR. OTTO VON FURTH, Professor Extraordinary of Applied Chemistry in the University of Vienna; authorized translation by ALLEN J. SMITH, Professor of Pathology and Comparative Pathology in the University of Pennsylvania. Pp. 635. Philadelphia and London: J. B. Lippincott Company, 1916.

THE book, containing twenty-five chapters, is based upon a series of as many lectures given to students of biochemistry. Naturally, therefore, it has the advantage of appealing to the larger

number rather than to the more or less limited class of technicians. Its value is perhaps best set forth in the beautifully chosen words of the translator: "The book has for its purpose the presentation of the subject of normal and pathological metabolic chemistry as a broad and connected whole. As a well-prepared and enthusiastic guide, thoroughly conversant with the topography, history, popular activities, spirit, and ambitions of the land through which he is conducting a group of thoughtful travelers, seeks to point out the salient features of the landscape and the accomplishments of the people, their success and their needs, and thus in the end leaves in the minds of the group before him a well-balanced idea of the region, so our author seeks to guide his readers through the living body, following the ingestion of great types of food, their digestion and absorption, pointing out here and there in the unknown field of intermediary metabolism the little which has become known, indicating their resultants, marking the points of departure of disease, presenting the big facts which we know in connection with the metabolic affections, and at all times suggesting the possibilities of further investigation and of orienting our thoughts into conformity with the general plan of nature's chemical performances. The book is thus rather a guide to thought than to the technicalities of the laboratory, and in this appeals alike to students, chemists, biologists, and physicians." There are many page references for those who desire more detailed information upon the subject at hand. Each chapter is divided into subheads, an arrangement which, at the same time, serves to emphasize the importance of the various parts which go to make up the whole and helps the reader to a better understanding of the subject. The book is justly commended as an "orderly and masterful delineation of the important features in the plan of chemical function in the animal economy."

Further than this little more need be said. Credit is due the translator for presenting the subject-matter in so lucid a manner, without attempting to adhere literally to the original text. The German work is widely known and appreciated, so that the present translation should meet with the approval it well merits.

H. D.

A Text-book of Pathology. By W. G. MacCallum, Professor of Pathology in the College of Physicians and Surgeons, Columbia University, New York City. Pp. 1084; 575 illustrations. Philadelphia and London: W. B. Saunders Company, 1916.

Dr. MacCallum has offered in this book his course of lectures at the College of Physicians and Surgeons, presenting the subject

in a philosophical treatise on general pathology from the standpoint of etiology. The various changes in the body are assumed to be due to some form of insult resulting in injuries expressed in various ways, the sequence of events being different in the various organs according to their physical and physiological character. The early part of the book is devoted to alterations in the physical and chemical characters of body fluids and the normal and pathological chemistry of cells and tissues. This is followed by several chapters on tissue reactions to insult and the basis of immunity. Nearly one hundred and fifty pages are then devoted to inflammation and repair. Having established the primary changes of diseased tissues the author then proceeds to detail the effect of various "types of injury" as he denominates them. Great emphasis is laid upon obstruction as a cause of later changes in the organs exposed, as for example the chain of events following stricture of the urethra and lithiasis or the various compensations necessary after failure of the heart in myocarditis or valvulitis.

To bacterial diseases and their effects two hundred pages are devoted, but little attention is given to the biology of bacteria and the properties by which microörganisms become pathogenic. The effects of animal parasites are briefly discussed.

The blood-making organs and the blood are next presented being classified and explained according to the author's classification. These chapters are followed by others on the glands of internal secretions which are presented rather from the standpoint of clinically observed results of hypo- or hyperactivity than from the pathological changes. In the succeeding chapters on the bones great attention is given to clinical changes and chemical alterations are emphasized. Tumors are presented under the old classification of tissue types and the book closes with a general discussion of tumors and what we know about their character viewed as aberrant tissue growths.

As a philosophical presentation of the reactions of body tissue to injury and the basic principles of tissue change the subject is well treated. The clinical side is emphasized, Dr. MacCallum is aware, but he maintains that pathology and clinical medicine are the same thing viewed from different angles. The book seems best suited to teachers in preparing their material, but it is to be feared that undergraduates will be confused by the grouping of numerous examples of tissue change under one heading and will surely miss the systematic grouping of organic changes under organs or systems.

At the end of each chapter several references are given that the reader may find other more elaborate, trustworthy articles.

The illustrations are almost without exception splendid, being well arranged and illustrative of their point. The book is well printed and free from typographical errors. H. F.

DIAGNOSIS AND TREATMENT OF SURGICAL DISEASES OF THE SPINAL CORD AND ITS MEMBRANES. By CHARLES A. ELSBERG, M.D. Pp. 321; 158 illustrations. Philadelphia and London: W. B. Saunders Company, 1916.

THIS is a splendid exposition of the diagnosis of surgical diseases of the spinal cord and its membranes. To begin with the book is very well gotten up on excellent paper and in readable print. Secondly, the reviewer knows of no work which is so freely and so well illustrated as this. Altogether in a book of 321 pages there are 158 illustrations, 3 of them being in colors. Most of the illustrations are from drawings made by that excellent artist Josef Lenhard, and are either of specimens or of active stages of operations. Besides there are a number of studies of patients and roentgen-ray photographs. The illustrations illustrate what the author is talking about and one can readily follow the different stages of a surgical operation with the greatest clearness. One cannot give too much praise to the excellence of this part of the work.

Dr. Elsberg has divided his subject matter in a logical and readable manner. His first division consists in the anatomy and physiology of the spinal cord and a symptomatology of surgical spinal diseases. The second division discusses the operations upon the spinal cord and spinal roots and in the last part there is a discussion of the surgical diseases of the spinal cord and membranes and their treatment. Nothing but praise can be given for the second and third divisions of this book. Dr. Elsberg's skill in spinal surgical operations is so well known that there is hardly any necessity of discussing the good work that has been presented in his book. One might differ with him as to the advisability of operating upon hematomyelia and syringomyelia or in his views regarding the operability of crush injuries of the spinal cord, but no one can find fault with his technic. Perhaps there is so much excellence it is out of place to criticize some phases of this work, yet the reviewer cannot altogether agree with the author in his method of examination of cases, which is hardly complete enough at least from the neurological standpoint, nor with his symptomatology of spinal cord diseases. When one considers, however, that this book is written primarily for the surgeon who is to operate on neurological cases the text is quite sufficient.

There has been a tendency among some surgeons who specialize in nervous work to emphasize the importance of having with their surgical knowledge a certain amount of neurological training sufficient to give them a working knowledge of the usual nervous diseases with which they come in contact. There is no doubt that a surgeon can do much better work when he knows a certain amount of neurology, but the difficulty is that some of these gentlemen are perhaps reaching too far in this direction. It would be not at all

inadvisable to have every neurological surgical case studied by a competent neurologist, for no surgeon if he has any work at all, has the time to give to the neurological side of medicine as much time as the latter deserves. Perhaps if this were done there would be better work and fewer operations. T. H. W.

OBSTETRICS, NORMAL AND OPERATIVE. By GEORGE PEASLEE SHEARS, B.S., M.D., Professor of Obstetrics and Attending Obstetrician at the New York Polyclinic Medical School and Hospital; Attending Obstetrician at the New York City Hospital. Pp. 734; 419 illustrations. Philadelphia and London: J. B. Lippincott Company, 1916.

THE author has set before us in a pleasing manner the essentials of obstetric theory and practice which he considers will be of most value to student and practitioner. Stripped of all irrelevant matter the text is shorter than in the usual volume on obstetrics, and hence a more easily handled book is obtained. The customary section on embryology has been omitted, as has also that traditional chapter on the development of fetal monstrosities, although sufficient description of these conditions is included in the section on complicated labor to enable the physician to recognize and correctly handle them.

The subject matter is fully abreast of the most recent advances in obstetrics, and while a certain amount of compilation has been necessary, a personal opinion of a moderately conservative nature adds interest to the volume.

The book is divided into four parts: The first part is devoted to normal pregnancy, labor, and the puerperium. The second part takes up the pathology of pregnancy and labor. The third part deals with obstetric surgery, and the fourth and concluding section considers the pathology of the puerperium.

The opening chapters describing the physiology of pregnancy clearly portray the profound changes of the maternal organism. The author lays due stress upon the diagnosis and clinical phenomena of pregnancy, commenting at length upon the scant attention paid to this most important phase of obstetrics, not only in the early stages when the diagnosis of pregnancy must be established, but in the later months when the position of the fetus and its relation to the maternal parts should be determined. The reviewer cannot agree with the statement that the serum diagnosis of pregnancy has a positive value. The rule for the management of pregnancy, labor and the puerperium are excellent. Not a little space is devoted to the subject of anesthesia in labor. In view of the danger to the

child from the morphin-scopolamin method, the author uses an initial dose of the two drugs, followed by a second dose of scopolamin. This he has found to produce a sufficient degree of analgesia in most cases. Should further anesthesia be required, ether is the agent of choice.

The author's views on the etiology of eclampsia are interesting. Nitrogen studies of the blood and excretions have shown a condition of suboxidation to exist in eclampsia. This he believes to be the basis for the symptomatology and pathology; on the strength of his views he has added inhalations of pure oxygen to the treatment of toxemias of pregnancy, not only as a curative but also as a prophylactic. The author believes in the immediate emptying of the uterus for antepartum and intrapartum convulsions.

The pathology of labor is fully considered. There are good chapters on pelvimetry, the diagnosis of fetal positions, and the use of the forceps. The subject of fetal mortality is discussed in some detail. Conservatism is the keynote of the chapter on the treatment of puerperal infection. Hemorrhagic conditions are taken up in an able manner from every standpoint.

The book is full of practical points in obstetrics, the illustrations, many from photographs, are well chosen, and the recapitulation of the more important directions at the end of many chapters is a valuable addition.

The volume which has been published posthumously will be a lasting memorial to the scholarship and high obstetric ideals of its lamented author. P. F. W.

THE PRACTITIONER'S ENCYCLOPEDIA OF MEDICAL TREATMENT. Edited by W. LANGDON BROWN, M.D., F.R.C.P., Assistant Physician to St. Bartholomew's Hospital, and J. KEOGH MURPHY, M.C., F.R.C.S., Surgeon to the Miller General Hospital for Southeast London. Pp. 874. London: Oxford University Press, 1915.

NINETY-SIX names are included in the list of contributors to this encyclopedia of medical treatment. These writers are Englishmen of varied repute, and of course the book for this reason has a very decided British atmosphere.

The work is divided into two parts: Part I includes methods of treatment, while Part II is devoted to agents in treatment. In the first part certain general forms of treatment are dealt with, and then the treatment for various disorders is arranged in a systematic way. In the second part are found the classified details concerning the action and use of different drugs.

In their preface the editors state that "despite the many excellent works on treatment that have already appeared, there is still need for

a *Practitioner's Encyclopedia of Medical Treatment* on the lines adopted by the contributors in this work."

The book is too large for easy reference and practical hard use. The binding is weak and the paper is rather coarse. Cheap production has no doubt been the aim of the publishers. A book of this sort must be prepared to meet rough handling. Much of the contents of this volume is the usual material found in such works and does not impress the reader as being the product of an especially thoughtful study of the subject matter at hand. At times remedies are advised which the Council on Pharmacy and Chemistry in this country has not sanctioned. This may not be an objectionable feature, still it hurts the average doctor in this country to have patented medicines suggested for his use. It is disappointing not to find any mention made of the newer ideas in the treatment of diabetes, gastric ulcer, and nephritis as set forth by our own workers.

The work, of course, gives a definite picture of treatment to the man who is in a hurry, and needs to know what he must prescribe. In this, however, it does not differ from a number of American works on the same subject, and indeed it is doubtful whether it serves this purpose quite as well as they do. It is a question whether, on the strength of being new and different, this book has justified its production. It has been issued since the outbreak of the present war, and for this the editors are to be congratulated. T. G. S.

COLLECTED PAPERS OF THE MAYO CLINIC, ROCHESTER, MINNESOTA. Edited by Mrs. M. H. MELLISH. Vol. VII (1915). Pp. 983; 286 illustrations. Philadelphia and London: W. B. Saunders Company, 1916.

THIS volume from the Mayo Clinic represents, as usual, the literary output for the current year (1915); it is noted, however, in a "Foreword," that, owing to lack of space, it has not been possible to include all the papers written by members of the Staff during the year: some are represented only by abstracts, and others have had to be postponed until the appearance of the next volume.

One feature about the present volume is new, and is worthy of commendation: this is the fact that the list of contributors, with which the volume opens, shows their status both in the "Mayo Clinic," and on the "Mayo Foundation, Graduate School, University of Minnesota." It was suggested by the reviewer, in commenting on last year's volume, that a lack of knowledge of their status sometimes militated against the statements of certain writers being accepted at what very likely was their true value.

The volume contains, as has been usual of late years, material

representing in fairly well-balanced quantity the various departments of surgery: surgery of the alimentary canal occupies about one-third of the volume, that of the urogenital organs a little over a tenth, that of the ductless glands (including a series of interesting papers on the spleen), and that of the head, trunk, and extremities approximately one-sixth each; while the remaining one-fourth consists of discussions of "technic" and "general papers." Included among the latter are several of Rosenow's weird bacteriological studies.

Although all, or almost all, of the papers in these annual volumes make their appearance elsewhere, and usually in advance of the publication of the Mayo Clinic volume; nevertheless, in their collected form they have come to be so convenient, if not necessary, to students of surgery everywhere that it is a satisfaction to believe that this publication is now established on a permanent basis, and that it will not die when the impetus and direction of the Founders of the Mayo Clinic shall have ceased to be active factors in its preparation; as is not the case, we regret to learn, with the publication from a sister clinic, which after a brilliant but meteoric career, is brought to an untimely end by the lamented death of its talented and indefatigable founder. A. P. C. A.

MEDICAL AND VETERINARY ENTOMOLOGY. By WILLIAM B. HERMS, University of California. Pp. 350; 228 figures. New York: Macmillan Co.

IN this book is found a systematic treatment of insects and other arthropods which may be concerned in causing or in transmitting human or animal diseases. It has not been the intention of the author to produce a comprehensive treatise, but rather a practical manual for the use of students and others immediately interested in the subject. No bibliography is given and references to the literature are not extensive. In Chapters I–V are considered questions of a general character, including insect anatomy and methods of disease causation. Following chapters take up the application of these matters to the various groups of arthropods systematically. The longest treatment is naturally accorded the Diptera, sixty-three pages being devoted to the mosquitoes and one hundred and sixty-six to the flies. There are numerous illustrations, a large proportion of which are reproductions of photographs. Some of these are good but many are unsatisfactory because of harsh lighting, resulting in lack of important detail. The treatment of the subject matter is thorough and clear without too extensive uses of "cases" and their uncritical details. For the convenience of those who wish to familiarize themselves with the

various animals involved there are descriptions, and keys for the larger groups.

A brief statement of the treatment accorded the mosquitoes will serve to give an idea of the character of the book. First there is an account of the systematic position of these insects with emphasis on the characters which differentiate them from similar appearing species. Then follows their life-history and sexual differences. The distinctive characters and behavior of the important species of disease-carrying mosquitoes, together with an extensive key for identifications, closes the chapter. Mosquitoes as disease bearers forms the subject next considered, and here the details of this relation are treated at length. The final chapter dealing with these insects is devoted to practical means for their control, including instances of actual expenditures for various conditions. In a similar way the case of the house fly is taken up at length. While especial emphasis is sometimes placed upon the needs and circumstances of the Pacific coast region the book is one which will make a general appeal and will prove valuable to anyone concerned in the prevention and cure of diseases caused by our insect enemies. McC.

GOULD'S PRACTITIONER'S MEDICAL DICTIONARY. Revised and edited by R. J. E. SCOTT, M.A., B.C.L., M.D., of New York. Third edition. Pp. 962; 70,900 words. Philadelphia: P. Blakiston's Son & Co., 1916.

THE third edition of this dictionary appears with a flexible binding and weighs two and a quarter pounds. The words it contains are those generally used in medicine and the allied sciences. Their definitions are concise and clear. As far as it is possible to say after a brief period of use, these words include among their number all of the terms found in recent medical literature. It is a dictionary at a reasonable price for those who are satisfied with non-detailed word meanings. T. G. S.

THE KINETIC DRIVE; ITS PHENOMENA AND CONTROL. By GEORGE W. CRILE, M.D., Professor of Surgery at the Western Reserve University. Pp. 71; illustrated. Philadelphia and London: W. B. Saunders Company, 1916.

As stated in the prefatory note, "This lecture is in effect an epitome of a monograph in preparation which will offer the complete experimental evidence upon which these themes and postulates are founded." The book represents in printed form the author's 1915

Carpenter lecture before the New York Academy of Medicine; it contains some beautiful photomicrographs, but only stimulates the hope that the promised monograph may soon appear, so that we may know what actual basis there may be for an attitude of dogmatism which, so far as the published evidence goes—we use Dr. Crile's own word—is "unwarranted." J. E. S.

Diagnose and Therapie der Gonorrhoe beim Manne (Diagnosis and Therapy of Gonorrhea in the Male). By Dr. S. Jessner, Sanitätsrat in Königsberg. Second revised edition. Pp. 169. Würzburg: Curt Kabitzsch, 1916.

In this monograph, covering one of the most discussed but least progressed subjects, therapeutically, in genito-urinary diseases, the author has presented a commendable work, of value both to students and practitioners, in which the anatomy of the urethra and its appendages, the symptomatology of gonorrhea and its complications and their respective treatment is detailed.

The critic in his review is conscious of the realization that there is nothing new which might prove useful in the treatment of this disease. Indeed, criticism should be offered that the work, useful as it is only for students and practitioners, not expert in the treatment of gonorrhea and its complications, would be enhanced by the addition of a few illustrations descriptive of the best type of therapeutic armamentarium. Moreover, it should be noted that no mention is made of operative procedures of well-recognized utility and merit, not infrequently necessary in the proper treatment of prostatitis, spermocystitis, epididymitis, etc.

Although biological products play a restricted role in the treatment of gonorrheal affections, they are, nevertheless, of much accessory value both in the pure as well as the mixed chronic complications. The author describes the administration of gonococcic bacterin (Arthigon) in arthritis, but fails to mention antigonococcic serum, an agent of greater potency and value in metastatic or systemic affections, particularly those involving the serous membranes, as synovitis, pleurisy, etc. B. A. T.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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The Volume of Urine in Young Healthy Adults on a Constant Diet.—ADDIS and WATANABE (*Jour. Biol. Chem.*, 1916, xxvii, 267) have recorded observations on the volume of urine per diem in healthy young adults placed on a constant diet, in which the fluid intake was measured. The authors find that the volume of urine in normal individuals is extremely variable for any single day or part of a day. The average volume of urine when the water intake was 2,070 c.c., varied in twenty individuals from 1,013 to 1,712 c.c. for a twenty-four-hour period, from 684 to 1,195 c.c., for the first twelve hours of the day, and from 501 to 788 c.c. for the first eight hours of the day. The percentage of the twenty-four-hour volume excreted during the twelve hours of the night did not exceed 47 per cent. in any subject.

A Rapid Method for the Diagnosis of Renal Tuberculosis by the Use of the Roentgen-rayed Guinea-pig.—MURPHY and ELLIS have shown (*Jour. Exp. Med.*, 1914, xx, 397) that white mice which have been exposed to the roentgen rays are much more susceptible to bovine tuberculosis than normal animals, a fact which they attribute to destruction of lymphoid tissue. This observation suggested to Morton (*ibid.*, 1916, xxiv, 419) the use of the roentgen-rayed guinea-pig in the diagnosis of renal tuberculosis, in an attempt to shorten the time required (five weeks) in this well-known method of diagnosis. The author finds that the lymphoid cells of the blood of the guinea-pig can be made largely to disappear from the circulation by a single massive exposure to roentgen rays. "The animal was placed in a pasteboard box of such size that it could not move around and then radiated for a period of ten minutes with the Coolidge tube, the target being twelve inches

distant from the base of the box. A 5 milliampère current was passed through the tube, backing up eight and one-half inches of spark between points. The Snook interrupterless type of machine was employed. No aluminum or leather filters were used." One to two cubic centimeters of urine were injected intraperitoneally, and after ten days the guinea-pigs were killed and examined. Ten patients with renal tuberculosis furnished material for the tests, and it was found possible by means of the roentgen-rayed guinea-pig to secure a positive result in seven to ten days. Apparently, the test works as well when the guinea-pig is exposed to roentgen rays immediately after inoculation. As in normal (unexposed) guinea-pigs the tubercles are most numerous in spleen, mesenteric lymph glands, and liver.

Pancreatic Diabetes in the Dog.—(I) The Influence of Alkali and Acid upon the Glycosuria and Hyperglycemia. MURLIN and KRAMER (*Jour. Biol. Chem.*, 1916, xxvii, 481) have studied the effect of the administration of alkali and acid on glycosuria and glycemia in depancreatized dogs. They find that sodium bicarbonate and potassium bicarbonate administered by stomach tube may be without immediate effect on the glycosuria and hyperglycemia. A bicarbonate given by mouth to a fasting depancreatized dog may even cause the reappearance of glucose in the urine after it had been starved out. Sodium carbonate (Na_2CO_3) may, on the contrary, reduce the sugar in the urine materially when given by mouth, and when given intravenously, it invariably does so, especially when added to Ringer's or Locke's solution to the amount of about 1 per cent. They furthermore find that the blood sugar does not undergo a compensating increase in percentage, even when the dilution of the blood is accounted for. Dilute hydrochloric acid given by mouth or subcutaneously to the depancreatized dog has, they find, just the opposite effect of alkali—increasing the sugar in the urine without affecting materially the nitrogen elimination—and without causing any effect on the blood sugar. (II) KRAMER, MARKER, and MURLIN (*ibid.*, p. 499), continuing the studies of Murlin and Kramer, have sought to determine the fate of the glucose retained as a result of the feeding of sodium carbonate to depancreatized dogs. They have demonstrated to their own satisfaction that it is not stored as glycogen and that it is not excreted by way of salivary gland, stomach or small intestine. The question whether it is oxidized will be treated in a later communication. (III) MURLIN and KRAMER (*ibid.*, p. 517) have investigated the influence of alkali on the respiratory metabolism of dogs after partial and total pancreatectomy. In partially depancreatized dogs which still have some capacity to oxidize glucose, the administration of sodium carbonate or sodium hydroxide with glucose is followed by a greater oxidation of glucose than when either is administered alone. Sodium carbonate itself causes but a slight increase in respiratory quotient, or none, whether administered per os or intravenously, to normal or diabetic dogs. Thus it seems that while sodium carbonate and sodium hydroxide alone cannot restore the lost function to an organism completely deprived of its ability to oxidize glucose, either substance can improve the capacity of the organism as a whole to oxidize glucose when this function is more or less crippled, although not completely lost.

SURGERY

UNDER THE CHARGE OF

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Bone Sutures in Granulating Wounds.—SCHMIEDEN (*Zentralbl. f. Chir.*, 1916, xliii, 779) says that he has been practising, in his military service, very extensive resections of joints, in order to avoid amputations in cases of severe joint injuries, with associated soiling of the wound and a wide opening in the overlying tissues. After conservative measures had failed he was able to save limbs by practising a wide opening of the knee-joint. All the ligaments were divided and the joint opened as for an excision. If the ends of the bones are fragmented, and secretions are retained in pockets between the fragments, an excision of the infected portions must be done. After the opening is made, the limb is kept in the flexed position by a bandage and soon afterward an extension apparatus is applied to keep the wound open. This treatment permits the wound to gradually clean itself. When this occurs and the fever disappears, the defect is opened up widely under lumbar anesthesia without regard to the discharge from the wound. Both bone stumps are separated by division through the granulation tissue and the ends sawed off smoothly. Holes are bored through to fix them firmly together. No effort is made to adapt or suture the soft tissue part of the wound. The whole limb is fixed in a plaster cast from the pelvis to the toes. An opening involving three-quarters of the circumference is left and is bridged over by metal splints. The discharge is taken care of by frequent dressings. In six to eight weeks enough bony union is usually obtained to permit the application of a second cast, which is often the last. The wire sutures may be removed in four to five weeks after operation, through the cast opening. The advantage of this method of treatment lies in the rapidity and certainty of healing, with very little loss in the length of the limb.

The Osteoplastic Activity of the Periosteum.—VOGEL (*Zentralbl. f. Chir.*, 1916, xliii, 794) reports the case of a five-year-old girl at the time of operation, in November, 1906, for a marked curvature of the left tibia from rickets. Notwithstanding the occurrence of primary healing, union of the bone did not take place. Passive hyperemia and repeated subperiosteal blood injections by the Bier method were also without success. December 19, 1907, the bone ends were united by wire sutures. Primary union without consolidation of the bone again resulted. May 8, 1908, the site of non-union was freely exposed, the periosteum elevated on the proximal and distal sides, the wire suture and all infragmentary callus removed, and on both sides of the tibia a plate of paraffin, $2\frac{1}{2}$ cm. long, $1\frac{1}{2}$ cm. wide, and 2 mm. thick, was so

placed under the periosteum, that the space between the bone ends was bridged over. The wound was closed and a fixation dressing applied and primary union resulted. After three months there was a certain degree of but not absolute union. Vogel did not see the child again until the autumn of 1915. The previously treated tibia was then firmly united, but at the site of operation, it was bent into the varus position with massive bone thickening. On January 1, 1916, the curve of the tibia was again corrected, this time by a wedge-shaped osteotomy. The following conditions were found: At the highest point of the bone thickening, between the callus and the overlying periosteum, lay the two pieces of paraffin, unchanged since they were depositited there eight years before. They were entirely loose, not adherent to the periosteum or bone, and were readily pulled out by forceps. The paraffin, carefully dissolved, showed by the microscope, no foci of organization. It was exactly like a control piece of paraffin. Vogel says that the paraffin, by putting the periosteum under tension (as by the Bier subperiosteal blood injections) excited the periosteum to callus formation.

A Contribution to the Operative Treatment of Forearm Synostosis (Fracture-Callus).—Schlapfer (*Deutsch. Ztschr. f. Chir.*, 1916, cxxxii, 225) discusses the subject of synostosis between the radius and ulna, acquired and congenital, based upon the results of two operations on one case. The first operation, performed ten minutes after the accident, was unsuccessful, the callus bridge between the radius and ulna was chiselled through in its whole length, after which the supination of the forearm was complete, it having been fixed in pronation from the accident to the time of this operation. Nearly two years later there was no pronation of the forearm and the roentgen ray showed that the callus union of the two bones had reformed. A second operation was then done. With hammer and chisel the callus was so freely removed that the forms of the two bones were restored to the normal. The radius was then wrapped in a fat-fascia flap taken from the thigh, which was fixed in position by catgut sutures. The muscles were sutured by catgut, the subcutaneous tissue and skin also being sutured. After the operation, pronation and supination were rather free. Primary healing occurred. Passive movements were begun on the third day. When the patient was discharged, seventy-two days after operation, there was no active pronation or supination but, passively, these movements were possible to about 25 degrees. The roentgen ray showed normal configuration of both bones. A few bone splinters left in the soft tissues were in the process of absorption.

The Surgical Uses of Ozone.—Stoker (*Lancet*, October 21, 1916, p. 712) says that the first 21 cases treated by oxone at the Queen Alexandria Military Hospital cannot be regarded as anything but satisfactory from every standpoint, humanitarian, scientific, or economic. The cases were, for the most part, those of cavities and sinuses in the femur and tibia. It is the experience of those who have seen a great deal of war surgery that such cases obstinately resist treatment and are apt to remain unhealed for months and years. The treatment consists of the application of ozone to the affected parts; it is, there-

fore, necessary to have an apparatus for generating ozone which shall be portable and easily worked. Stoker uses the Andriolis ozonizer. It is called into operation by a four volt battery animating a ¼-inch sparking Rhumkorff coil. The oxygen passes from a cylinder through the ozoniser, and in doing so comes in contact with a metal armature, the effect of this being to transform the oxygen into ozone. A tabulated statement showing the effects of the treatment in 21 cases with chronic bone sinuses is very favorable to this method. The properties of ozone are, are far as one can say at present, three: It is a strong stimulant and determines an increased flow of blood to the affected part. It is a germicide, which destroys all hostile microörganic growth. As the French chemist, Hennocque, has shown, it has great powers in the formation of oxyhemoglobin. The ozone is applied on the wounded surface or to the cavities and sinuses for a maximum time of fifteen minutes, or until the surface becomes glazed. Ozone has the particular power of disclosing dead bone, foreign bodies, septic deposits, etc. Stoker believes it does this by destroying the granulations and micro-organic growths (presumably unhealthy) that are found in close contact with septic deposits, foreign bodies, or dead bone. Wounds and sinuses, etc., are washed twice daily with boiled water and a dressing of dry gauze is applied. It must be observed that at first ozone causes an increase of the discharge of pus; later on the pus is replaced by clear serum, which at a still later stage becomes colored reddish or pinkish. In open wounds it is necessary to strip off the parchment-like film surrounding the edges, which is composed of oxydized serum. This is easily effected by applying a hot compress for fifteen or twenty minutes, after which the film can be easily peeled off with a dissecting forceps.

THERAPEUTICS

UNDER THE CHARGE OF

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Autogenous Defibrinated Blood in the Treatment of Bronchial Asthma.—KUHN and EMSHEIMER (*Arch. Int. Med.*, 1916, xviii, 445) say that inasmuch as bronchial asthma is due to sensitization by a foreign protein, immunization by injection of the causal protein should be of benefit. They believe that with each attack of asthma there occurs a sudden or gradual liberation into the circulating blood of the protein which excites the attack. If blood is withdrawn during the attack it presumably contains the toxic protein or antigen. Repeated injections of this defribrinated blood are made subcutaneously at varying intervals. The quantities of antigen contained in each injection are so minute as to create a very small amount of antibody each time,

and never to result in an attack. Thus the tolerance of the body for the protein may be enhanced. Naturally in an ideal course of treatment it would be desirable to obtain the blood each time just prior to or early during an attack of asthma, since it is assumed that it is time that the antigen is in the circulation in the greatest amount. It is possible that the benefit from the treatment may rest on an empirical basis. It can be contended that the mere withdrawal of blood from the circulation and its reintroduction subcutaneously is not sufficient to produce a marked biologic effect on the involuntary muscles. It may also be said that the original presence of antigen in the circulation should also serve to immunize the individual. But this does not take place in asthma, whereas the clinical results from the treatment would seem to permit of the foregoing interpretation. The authors state that six successive patients with bronchial asthma, treated by repeated injections of autogenous defibrinated blood, have shown definite improvement as indicated by diminution in frequency and severity of attacks, gain in weight, increased ability to work and improved subjective symptoms. The results in these cases are promising enough to justify a continuation of the treatment and to find in what proportion of the cases it is of benefit, and to what degree.

A Study of Serum Salvarsanized in Vitro.—SWIFT (*Jour. Exper. Med.*, 1916, xxiv, 373) says that, following the introduction of intraspinal injection of serum in the treatment of patients with syphilis of the central nervous system, numerous workers have attempted to inject intraspinally salvarsan or neosalvarsan in weak dilution. When more than 1 mg. has been repeatedly injected, several observers have noted symptoms of myelitis in the lower segment of the cord. Marinesco and Minea have observed that neosalvarsan diluted with serum is less irritating than when diluted with normal sodium chloride solution. Fordyce and Ogilvie advise that only a fraction of a milligram of salvarsan be mixed with the serum for intraspinal injection. Clinical evidence seems, therefore, to indicate that only small amounts of salvarsan or neosalvarsan can be safely injected into the subdural space. The main objection to subdural therapy of cerebrospinal syphilis has been that the serum injected contained such small amounts of salvarsan. Obviously it is necessary to keep the amount of any therapeutic agent below the injurious dose. Therefore, with the evidence at hand only small amounts of the drugs at our disposal can be used. The object then must be to use them in the least injurious and most potent form. From the evidence brought forward by Swift this would be the addition of small amounts of salvarsan or neosalvarsan to the serum of salvarsan-treated patients. This serum should be allowed, preferably, to remain in contact with the clot overnight, and should be heated after the addition of the salvarsan. Although this technic is complicated it could be easily carried out in clinics where large numbers of patients are treated, or if the salvarsan is procurable in ampules containing small amounts so that dilutions for addition of the drug to the serum might be economically prepared. Swift summarizes his study as follows: addition of salvarsan to serum *in vitro* produces a spirocheticidal mixture which is increased in potency by heating. The heated serum of salvarsan-treated patients is more spirocheticidal if it has been in contact with the

clot overnight than if it has been separated immediately after coagulation. This is not true with the serum from blood which has been salvarsanized *in vitro*. The addition of salvarsan directly to serum produces a more potent mixture than results from the serum from blood to which salvarsan has been added in equivalent amounts. The increase in activity of salvarsanized serum produced by heating to 56° C. is due in part to the removal of inhibitory substances in the serum and in part to a direct increase in spirocheticidal power in the heated salvarsan. Both salvarsanized and neosalvarsanized serum are rendered more spirocheticidal by heating. A more active spirocheticidal mixture is produced by mixing small amounts of salvarsan with the serum of a salvarsan-treated patient than with normal serum.

Immune Human Serum in the Treatment of Acute Poliomyelitis.—WELLS (*Jour. Am. Med. Assn.*, 1916, lxvii, 1211) says that the administration of immune serum in acute poliomyelitis is based on recognized principles of immunity. Because the lesions are not confined to the nervous system and because the lesions therein consist essentially of perivascular infiltration, intravenous injection of serum appears to be a rational procedure, either alone or in combination with intraspinal injection. Intravenous injections of serum should, if possible, consist of doses of from 50 to 100 c.c. or more daily. Following intravenous or intramuscular injections of serum, spinal fluid should be withdrawn. Intraspinal injections of serum usually produces an increase in the number of the leukocytes with increase in the proportion of polymorphonuclear cells in the spinal fluid. In the fifteen cases that Wells treated no ill effects followed the use of serum, either by intravenous or intraspinal injection. In all cases, after intravenous injection, and to a less degree after intraspinal injection, a noticeable improvement usually occurred, which, unfortunately, however, in some cases was only transient. Early administration of the serum is urged, necessitating therefore an early diagnosis of the disease; in severe cases late administration of the serum has produced little if any noticeable influence on the course.

The Action of Benzol.—WEIS ROTTEN, SCHWARTZ and STEENSLAND (*Jour. Med. Research*, 1916, xxxv, 63), in a previous communication, reported experimental work on the action of benzol by giving rabbits two or more daily subcutaneous injections of equal parts of olive oil and benzol. It was found that in all cases in which the animals survived the primary fall in the leukocyte curve there followed a primary rise which reached a normal level and in many instances reached the original level. This primary rise was always independently of any further injections, followed by a secondary fall, which in turn was followed by a secondary rise to a normal level. In the secondary fall the leukocyte curve almost invariably reached a level nearly as low as the primary fall, and in some instances even lower. Further work has given similar results. The authors' experience indicates that the mortality during the secondary fall is practically as great as during the primary fall. In all animals surviving the secondary fall there occurred a return of the leukocyte curve to a normal level, and there was no evidence of any subsequent falls. As a descriptive term appropriate for indicating

the occurrence of the two periods of leukopenia above described Southard has suggested the term "diphasic leukopenia." For the first period, the authors suggest the term "Protophase," this extends from the onset of the primary fall and ends with the termination of the primary rise. The second period denoted "Deuterophase," extends from the onset of the secondary fall and ends with the termination of the secondary rise. The authors found this latter phase, following subsequent sets of subcutaneous injections of equal parts of olive oil and benzol in rabbits the same in every respect as that following a first set of injections.

Syphilis of the Nervous System.—FORDYCE (*Med. Rec.*, 1916, p. 575) in outlining the course to be pursued in the treatment of syphilis of the nervous system considers that the best procedure is to give provocative injections of salvarsan to patients with a negative blood and a positive spinal fluid, and take the Wassermann at stated intervals. If the Wassermann remains negative, subarachnoid treatments may be begun at once. When both blood and spinal fluid are positive, two or more injections of mercury should precede the intravenous administration of salvarsan and after two or three doses of the latter the intraspinal treatments are begun, supplemented by intravenous injections. In paresis, intraspinal injections are best begun after the first intravenous treatment, while the intervals between doses are regulated by the patient's reaction. Where subdural injections are well borne, they may be given in a series of four to six, one or two weeks apart with a rest period of four to six weeks before giving another course. Ogilvie's modification of salvarsanized serum is now used by Fordyce, in which method salvarsan is added directly to the blood serum. Blood serum removed indifferently from patients acts as well as autogenous serum, and the most important step in the technic, next to absolute asepsis, is the use of a nearly neutral salvarsan solution. The blood is removed from an arm vein and centrifugalized to secure complete removal of red cells. To 8 or 10 c.c. of this serum 0.05 to 0.5 mgm. of salvarsan is added and the mixture is incubated at 37° C. for thirty minutes. General paresis patients tolerate larger doses than those with tabes or other forms of cerebrospinal syphilis. The initial dose for tabetics should be 0.05 to 0.1 mgm., depending on the bladder involvement and the amount of pain present, and the quantity is gradually increased up to 0.2 to 0.3 mgm., if the patient will tolerate it. Activation of the lesions after the first injection is not a contra-indication, but calls for care. There seems to be no limit to the number of injections that can be given. Cure, amelioration or failure is dependent upon the extent and type of the morbid process. Success depends largely upon whether the morbid process is an active meningeal inflammation or a degeneration of essential nerve structures. Active inflammation with a strongly positive fluid gives a hopeful outlook, while degeneration with atrophy and sclerosis, with negative or weakly positive fluid, does not present so encouraging a prognosis. In his conclusions Fordyce states that all patients at the end of the first year of their infection should have a spinal puncture, whether or not they have any signs of the disease. If the fluid is negative to all tests, they may be assured that there is little danger of later development, whereas a positive

colloidal gold test with persistent Wassermann in high dilutions points to an impending paresis. In the great majority of patients there is little risk attending either intravenous or intraspinal treatment. In diseases of the central nervous system it is not altogether a harmless procedure according to Fordyce and it cannot be emphasized either too strongly or too frequently that every precaution be carefully carried out in regard to preparation, size of dose and sufficient rest in bed after treatment.

The Indications for Splenectomy in Certain Chronic Blood Disorders.—Balfour (*Jour. Am. Med. Assn.*, 1916, lxvii, 790) says that the success of splenectomy in splenic anemia, with associated splenomegaly and severe anemia, has led to splenectomy in other diseases in which splenomegaly and anemia are characteristics. One of the most interesting of these is the syphilitic spleen; good results have followed splenectomy in three cases of this form of syphilis. All the patients had gummas in the liver, and in the spleens removed the spirochete could be demonstrated in large numbers. It was also a clinical observation that although the virulence of the infection could be more or less controlled by antisyphilitic treatment, it was not eradicated. From the foregoing facts, the conclusion may be drawn that the spleen picks up the spirochetes and harbors them, and this conclusion is supported by the surgical observation that removal of the spleen, followed by antisyphilitic treatment, results in prompt and permanent relief. The remarkable results following splenectomy in splenic anemia and hemolytic jaundice, particularly the latter, appear to have provided the basis on which Eppinger and others have suggested that similar surgical treatment might prove of value in pernicious anemia. Balfour believes that splenectomy should be considered in every case of pernicious anemia in which the diagnosis has been established and all possible etiologic factors which might be independently remedied have been excluded. The failure of other means to combat the disease, the previous fatal prognosis, and the low operative mortality are strong arguments in favor of splenectomy. The activity of the disease is an important consideration in discussing the advisability of operation. Splenectomy should be undertaken with hesitation in acute stages of pernicious anemia and especially with a falling blood picture. The operation cannot at the present time be advocated when cord changes and other permanent pathologic processes mark the terminal stages of the disease. Moreover, as already suggested, if it is not feasible to tide a patient over the critical periods by transfusion, splenectomy is contraindicated. Definite statements based on the qualitative blood picture cannot be made, but if the hemoglobin is under 25 per cent. and cannot be raised, operative treatment is of considerable risk and has doubtful results. The extent of the disability of the patient must of course be carefully considered. If a patient with every evidence of the disease is able to carry on his usual occupation, splenectomy cannot be strongly advocated, yet these may be the very patients in whom best results may be obtained. The operation may be urged more legitimately when the patient is unable to do his work or is a chronic invalid.

PEDIATRICS

UNDER THE CHARGE OF

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Fainting Attacks in Children.—HUTCHINSON (*Brit. Jour. Child. Dis.*, 1916, xii, 161) reports a study of ten cases of fainting attacks in children in an out-patient clinic. It was noticed that both sexes suffer from the attacks but girls rather more frequently than boys. Occasionally they date from early life but usually do not appear until the fifth year or later and are commonest after school age. In general features the attacks are similar in all cases. The child is observed to "go white" and may fall down but does not lose consciousness entirely although it is often dazed or even only semiconscious. Occasionally vomiting or retching occurs but in no case was urine voided involuntarily. Attacks last from a few minutes to half a hour and pass off gradually often followed by a headache. The commonest time for the attacks to occur seemed to be before breakfast or while the child was getting ready for school. Of the children examined many were nervous and dyspeptic but in a considerable number the general health was quite good and the appearance flourishing. There seemed to be no relation between the attacks and any previous disease. The author observed one attack in a boy he was examining. The boy became pale and giddy, the pulse slow and feeble, the heart sounds toneless. He was quite conscious but somewhat confused and revived gradually after lying down. Hutchinson could discover no cause for the susceptibility of these attacks, but over-strain at school seems to play a part in some cases. There is no evidence that the heart is primarily responsible and the origin is probably a nervous one primarily. Change of air to the seaside, removal from school, strychnin as a tonic and attention to digestive organs include the treatment which usually clears up the attacks speedily.

Meningitis in the Newborn and in Infants under Three Months of Age.—KOPLIK (*Arch. Pediat.*, 1916, xxxiii, 481) in discussing meningitis in the newborn says that this condition is often overlooked at first because the nervous and physical reaction to irritation in the newborn is extremely slow and obscure. Many cases of primary meningitis are only suspected as such after developing sufficiently to give signs of cerebral pressure. In the newborn even with cerebral symptoms the body remains limp. The symptoms most characteristic of meningitis in the newborn are, convulsions, repeated at first and, if recurring, as is rather characteristic, do so two to four days after birth. Convulsions are accompanied by rather high fever, dropping gradually and after the first week often running but one or two degrees above normal. Periods of constant crying and restlessness with normal condition of the bowels is characteristic. The fontanel may show

bulging only days or weeks after the onset, giving at first no clue. Before fluid accumulates there is no MacEwen sign. Kernig's sign is usually absent as is Brudzinski's sign and cannot be elicited until a much later period. Rigidity of the neck is elicited at first rarely, or not at all, until weeks postpartum. Very characteristic of purulent cases are convulsions accompanied by a fall in temperature and symptoms of collapse with cyanosis resembling chills. Constant vomiting in the form of regurgitation irrespective of feeding time is characteristic, as is a peculiar groaning noise made in breathing. The temperature may, after a week, drop to normal and stay there. Tetany is of even rarer occurrence than meningitis while in meningeal hemorrhage from pressure there is no fever, and cyanosis and respiratory signs would be present. Even a suspicion of meningitis would indicate lumbar puncture.

Creolin in Scabies in the Infant.—MONTGOMERY (*Arch. Pediat.*, 1916, xxxiii, 525) recommends creolin as an effective innocuous antiseptic which is an admirable non-irritating parasiticide adaptable to the treatment of scabies in the infant. Scabies in the infant tends to spread all over the body and at this age is frequently associated with eczema and pyogenic skin infection. Sulphur, while probably the best remedy for scabies, is highly irritating to some skins and often very irritating to the sensitive skin of the infant. Balsam of Peru is an excellent remedy but difficult to obtain absolutely pure, while betanaphthol as a salve is a fine antiscabetic, but unfortunately in several instances has caused death when employed for scabies. Creolin, however, offers the best substitute for sulphur which sometimes leaves an irritation of the skin long after the scabetic condition has subsided. The following prescription is given, being the formula used by Dr. Werther of Dresden. ℞ creolin, 10.00; sapo viridis, 30.00; adipis benzoati ad. 100.00. M.—Sig. Rub in once a day. The green soap adds to the penetrating qualities of the preparation but it is not a necessary ingredient and may be undesirable as drying and irritating to the tender infant skin.

A Clinical Study of Postnasal Infections.—BAXTER (*Arch. Pediat.*, 1916, xxxiii, 729) made a study of 60 cases of postnasal infections occurring during an epidemic in 1915. Five of the cases were complicated by acute hemorrhagic nephritis. Only 3 cases of this series were complicated by an acute tonsillitis. The cases range in age from one to eight years. The diagnosis of postnasal infection was made from the presence of constitutional symptoms of an infectious condition supplemented by negative physical findings in all parts of the body except on the part of the nasal passages. The symptoms were either a mild coryza or obstruction to nasal breathing with the anterior nares free and a mucopurulent discharge from the postnasal space. In some cases there was adenitis of the lymphatic glands behind the sternomastoid muscle which drain the postnasal space. There was no glandular suppuration in any of the cases. The duration of the infection, exclusive of complications was from one to three weeks. No complications on the part of the heart were observed. Five of the cases were complicated by acute hemorrhagic nephritis. This occurred mostly in the

older children of from four to eight years. There was involvement of the middle ear in more than 75 per cent. of the cases, and this was especially frequent in infants under two years. The cases studied bacteriologically did not show the prevalence of the streptococcus, but usually showed a pure culture of staphylococcus. In involvement of the middle ear it is important not to be hasty in doing a paracentesis, especially in infants under two years. In the present series the results obtained without paracentesis were practically as good as those where a paracentesis was done. It is not good treatment to do a paracentesis in every case of otitis media. Besides general treatment the author employs the following: Irrigation of the ear, when involved, with a warm solution of boric acid or carbonate of soda two or three times in twenty-four hours. Two per cent. carbolic acid in glycerin instilled into the ear at intervals of three hours. Irrigation of the nasal passages with warm alkaline solution under gravity pressure twice a day. The cases of nephritis were given the usual treatment for this condition. Fisher's solution was used per rectum by the drop method and instillation in 4 cases. The immediate recovery occurred in about four weeks and the ultimate clearing up of the urine in from two to four months.

OBSTETRICS

UNDER THE CHARGE OF

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Biochemical Function of the Decidua.—GENTILI (*Annali di ostetricia*, No. 2, 1916) has studied the biochemical functions of the decidua with special regard to the formation of lipoid material. The article is accompanied by microscopic illustrations showing the alteration in cells in various conditions of disturbed metabolism. His researches show that under certain conditions the decidua may contain a considerable proportion of lipoid bodies without passing into a state of actual fatty degeneration.

Backward Displacement of the Pregnant Uterus.—In an article upon this topic in general, MCCANN (*Brit. Med. Jour.*, July 1, 1916) states that when the pregnant uterus is displaced backward it will sometimes return to the normal position. To secure this result without interference the patient must be kept at rest in bed and the catheter used regularly. Retention of urine is one of the most frequent of the conditions, and one of its most serious complications. In making efforts to replace the uterus the greatest gentleness must be employed, as such efforts frequently result in abortion. When the pregnant uterus is fixed backward by adhesions it may be necessary to open the abdomen and free the adhesions. In two cases treated, one patient went

to term and was successfully delivered, the other aborted four weeks after operation. If other methods be thoroughly used operation will rarely be necessary. In the experience of the reviewer rest in bed and the use of the catheter may to advantage be supplemented by having the patient take the knee-chest posture night and morning. Attendance of a nurse is very desirable, and she should see that when the patient takes the knee-chest posture air enters the vagina freely. To secure this the parts should be separated by the nurse, or a medium-sized cylindrical rubber speculum should be inserted. Where the uterus does not go back readily but is mobile, tampons of carded wool run out of 0.5 per cent. lysol solution have been found useful.

The Abderhalden Test for Pregnancy.—In Bossi's clinic at Genoa, CARLINI (*Annali di Ostetricia*, No. 3, 1916) has tested the Abderhalden method by dialysis and by the method of color estimation. He finds, as have many others, that the method of dialysis frequently gives the positive result where there has been no pregnancy, and especially in diseases of the uterus and ovaries. In the method which uses the estimation of color he could come to no definite positive conclusion. In general his results coincide with those of others, that even with the most careful technic the reaction is of very limited application.

Pelvimetry during Pregnancy.—PONZIO (*Annali di ostetricia*, No. 3, 1916) has studied the examination of the pelvis during pregnancy by the use of the roentgen ray. He illustrates his method by a picture of the pelvis viewed by the fluoroscope, and illustrates a method of computation for estimating the true conjugate; also the distance between the pubes and the coccyx. He refers to the work of Manges, and his conclusions and method. To those who are practising the use of the roentgen ray for diagnosticating purposes, this paper will be of value.

Surgical Replacement of the Retroposed Uterus.—BISSELL (*Am. Jour. Obst.*, July, 1916) describes his method of permanently curing backward displacement of the uterus, and gives the results of pregnancy and labor subsequent to the operation. His present method consists in grasping the round ligament near its center with two instruments 2 cm. or more apart. Gentle traction is made, and the tense portion of the ligament between the forceps is split through its middle longitudinally, the point of the knife passing down between the surface of the broad ligament. Each split portion of the round ligament is now grasped with forceps, and the other instruments released. Straight scissors are next passed through the split in the round ligament and forced down between the layers of the broad ligament, and opened several times to separate the surfaces, and with the same scissors the longitudinal division of the round ligament is continued on the distal side to within close proximity of the infundibuliform process of the ligament, and on the proximal side to its uterine insertion. The anterior split portion of the round ligament is now severed about 1.5 cm. from the infundibuliform process, and cut away from its broad ligament attachment. The posterior split portion is severed about 1.5 cm. from its uterine insertion, and cut away from its broad ligament

attachment. The cut end of each remaining split portion of the round ligament is sutured to its corresponding cut end with silk or linen, and the apposing lateral surfaces of the split portions are held together by fine catgut at their middle. The round ligaments are thus shortened about 2.5 cm., and larger than previously in diameter. The middle of the posterior surfaces of the broad ligament is now folded on itself and penetrated at its base with a suture of chromic gut, avoiding the Fallopian tube. When this suture is tied the posterior surface of the broad ligament is narrow, and the cut edge of the fold united by continuous catgut suture. The same thing is done on the anterior surface of the broad ligament, avoiding the uterine artery. This narrows the entire ligament. The combined effect of shortening the round ligaments, and narrowing the broad ligaments brings the uterus into its normal anterior position. When the uterus is unusually large and heavy a temporary suspension by chromic catgut is added to this portion. He has studied the results of this in 185 cases. In all there were 8 failures so far as the position of the uterus was concerned. In 7 cases he has had the opportunity of reopening the abdomen. In one of these patients the abdomen was opened more than seven years after the original operation, and adhesions found between the uterus, bladder, and anterior surface of the broad ligament. At the second operation the uterus and adnexæ were removed. After the operation the patient had given successful birth to three children. Fourteen women in this series have passed through labor in such operation, and 19 births have occurred. In 1 the uterus again became displaced backward; in 3 forceps were used; in 1 vaginal Cesarean section performed. One of the patients after operation for displacement had labor followed by complete prolapse, for which hysterectomy was finally done. One case aborted at the third month. The majority of testimony obtained by the clinical investigation of these cases is in favor of the operation.

The Significance of Syphilis in Obstetric Patients.—FULLERTON (*Am. Jour. Obst.*, July, 1916) believes that although the Wassermann reaction may be positive, that a patient who has had prolonged and thorough treatment for syphilis may marry after a reasonable time. He believes that the germs of syphilis may be living in the body of the patient without conveying infection. Salvarsan is useful in cutting short the first and second stages of syphilis, but mercury and potassium iodide are necessary for prolonged treatment. In pregnancy drugs given to the mother are conveyed to the fetus in the uterus. After birth the child is best treated by inunctions of mercury, the mother continuing her treatment, and nursing her child. In preventing the ravages of syphilis in parturient women, all women should be thoroughly examined, in each case the placenta should be accurately weighed and examined, and newborn children should be thoroughly inspected. In obstetric clinics the germs of syphilis should be sought for in all suspected cases by microscopic examination. Every effort should be made to follow up cases that show signs of syphilis.

GYNECOLOGY

UNDER THE CHARGE OF

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Role of Douglas's Pouch in the Production of Rectal and Uterine Prolapse and Rectocele.—JONES (*Boston Med. and Surg. Jour.*, 1916, clxxv, 623) believes that Zuckerkandl, Bardenhauer, Moschcovitz and others have demonstrated beyond question an important relationship between the posterior cul-de-sac and its lining fascia and prolapse of the rectum and associated organs. Clinically, Jones recognizes three forms of unusually deep cul-de-sac, the condition which he thinks favors prolapse. The first form is congenital; in it the peritoneum lining the deep pelvis is smooth and closely abherent to the pelvic walls, and the rectum, instead of standing out as a definite organ, is flattened against the sacrum and coccyx. It is with this type of cul-de-sac that prolapse of the rectum occurs in males and in virgins, and prolapse of the uterus and vaginal walls in virgins. The second form is acquired, occurring in multiparæ, as a result of overstretching of the deep pelvic fascia in pregnancy. Here the peritoneum is redundant and not adherent to the pelvic walls, and the rectum stands out distinctly in the pelvis. In the third form there is a small pouch between the rectum and vagina, reaching down to the levators, and usually causing a vaginal protrusion. It is probable, the author thinks, that in the first form the pelvic fascia, which should normally dip down into the cul-de-sac and line it completely, is wanting in this region; in the second form the fascia is present, but is greatly attenuated, while in the third form the fascia is present normally save for a small defect in the posterior portion, through which the intestines force their way to the depths of the pelvis. Jones considers all types of rectal, uterine and vaginal prolapse as hernias, presenting analogous mechanism of formation to hernias in other parts of the body. He reports having seen within the last two years four virgins with the congenital type of deep cul-de-sac. In one there was a prolapse of the rectum, in one a prolapse of the rectum and uterus with a large cystocele, and in the other two a prolapse of the uterus with rectocele. In order permanently to correct the trouble leading to these prolapse conditions, the author considers it necessary not merely to narrow the outlet of the pelvis or to suspend the bowel from above, but to close the hernial sac at what might be termed the internal ring as well. This is accomplished, to some degree at least, by obliterating the cul-de-sac with purse-string sutures of silk, the rectum being also attached to the pelvic peritoneum on either side up to the level of the promontory by silk sutures in the hope of getting support from the many attachments to the peritoneum. In the female the rectum is also sutured to the posterior surface of the vagina and uterus and a ventrofixation is done. The anterior wall of the rectum, being much stretched, must be drawn well up into the pelvis by a guide

suture placed as low as possible in the rectum, and fixed as high as possible. While it might seem that there would be considerable danger of injuring the ureters or great vessels in thus closing the cul-de-sac, Jones says he has never seen trouble from this source in a series of about twenty cases. While the closure of the cul-de-sac in this manner may seem to have little strength, since the sutures include probably nothing but peritoneum, its great value lies in the fact that it throws the weight of the intestines and the intra-abdominal pressure forward onto the symphysis, bladder, and anterior abdominal wall, while an open deep cul-de-sac allows these forces to come against the anterior rectal or posterior vaginal wall.

Etiology and Pathology of Non-tuberculous Renal Infections.—The theory is advanced by CABOT and CRABTREE (*Surg., Gynec. and Obst.*, 1916, xxiii, 495) that practically all renal infections arise as a result of hematogenous invasion of the kidney by the organism in question, these authors considering the ascending or lymphatic routes as practically negligible in importance. They have reached these conclusions following the study of a considerably series of kidneys presenting infections from organisms other than the tubercle bacillus. It has been generally believed in the past that coccus infections of the kidney are usually hematogenous in origin, but it has been rather generally assumed that bacillary infections reach the kidney by ascent from the bladder. This assumption Cabot thinks to be based wholly on its delightful simplicity, but entirely unsupported by scientific evidence. He sees no reason for denying a hematogenous origin for bacillary any more than for coccic infections; in fact, the former has been the more conclusively proven of the two, for the organisms have been repeatedly found in the blood and subsequently in the urine in cases of renal infection, whereas there are but few instances on record where cocci concerned in renal infection have been demonstrated in the blood. He believes also that the common pyelonephritis—mistermed pyelitis—of pregnancy and of children occurs only as a result of organisms reaching the kidney through the blood stream. In contradistinction to the generally accepted views, Cabot holds that the lesions produced by different types of organisms are more or less characteristic, those caused by the pyogenic group (cocci and pyogenic bacilli) differing essentially from those caused by non-suppurative organisms (colon-typhoid group). The former consists of perinephritic abscesses, capsular abscesses, capsulitis, cortical abscesses, septic infarcts, and diffuse suppuration; the latter of acute pyelitis, acute pyelonephritis, chronic pyelonephritis, and pyonephrosis. Infection of a kidney by organisms of both groups will cause a mixture of the lesions, this fact probably explaining the belief that the colon bacillus can produce abscess of the kidney. Cultures containing both colon bacilli and cocci will frequently be interpreted as showing only colon, as this organisms grows with great rapidity and soon obscures the colonies of cocci. The differences in the types of lesions produced by the two groups of organisms are of considerably more than mere academic interest, as Cabot points out, for they have an important bearing on diagnosis. Since the lesions characteristic of the pyogenic group are comparatively shut off from the lower portions of the kidney, and do not involve the pelvic mucous

membrane, pus is rarely found in any considerable amount in the early stages. The lesions of the non-pyogenic group, however, are situated chiefly in the renal pelvis, and result in early appearance of pus with microörganisms in the urine. There is also a marked difference in the effect on phthalein excretion. Infections with the pyogenic organisms involve chiefly the cortex and very little the convoluted tubules, having therefore little effect on the kidney function as measured by phthalein elimination; the chief lesions of the colon group, however, are in the region of the convoluted tubules, and produce sudden and profound changes in renal function. If, therefore, in the presence of clinical evidence suggestive of renal infection, the freshly drawn urine shows cocci in abundance, with a small amount of albumin, a few red blood cells, and many leukocytes or a little pus, with a normal or nearly normal phthalein excretion, the diagnosis of coccus infection is justified. If, on the other hand, examination of the urine shows many bacilli, a little albumin, and much pus, with marked diminution of the phthalein excretion, a diagnosis of colon bacillus infection is unavoidable. Since the suppurative lesions concern those parts of the kidney relatively inaccessible to drugs, their treatment must in the majority of cases be operative, but the lesions of the colon group, involving chiefly portions of the kidney which are relatively accessible to the formalin-containing drugs, a thorough trial of medical treatment in these cases is often advisable. It thus becomes evident that an accurate diagnosis between the two types of non-tuberculous renal infection is of great practical importance from the standpoint of therapy.

Severe Intraperitoneal Hemorrhage from Small Superficial Veins of a Myomatous Uterus.—A most unusual and very interesting case of a condition which very seriously threatened the patient's life has been reported by GERSTENBERG (*Zentralbl. f. Gyn.*, 1916, xl, 795). The patient was a nurse, aged thirty-nine years. While on night duty, taking care of a man whom with great difficulty she was able to lift or move, she was seized one night a few days before her menstrual period with several fainting spells. She attributed these to her run down condition, with the hard work that her night duty entailed. The next night she had another, more severe attack, whereupon she took an alcoholic stimulant and went home to bed, where she was found the next morning in a state of collapse. On examination by Gerstenberg at this time the uterus was found to be small and retroverted, with a hard, roughly spherical tumor somewhat larger than a fetal head, lying above it. The diagnosis was obviously a subserous myoma; the advice given was rest and building up measures, to be followed later by operation. The next morning the author was urgently summoned again, and found the patient pulseless and presenting unmistakable signs of severe internal hemorrhage. By means of active stimulation and abdominal compression it was possible to transport her to the clinic, where the abdomen was immediately opened, practically without anesthesia. The abdominal cavity was found filled with an enormous amount of dark, almost entirely uncoagulated blood, apparently of venous origin. A rapid search of the tubes, ovaries, fibroid tumor, bladder, and intestines failed to show any source of the hemorrhage. Only after throughly cleansing the pelvis and drawing the uterus and

tumor well forward were two tiny slits found in the peritoneum covering the right posterior aspect of the uterus. No blood was coming from them, but they were immediately over small veins, and showed a few attached blood clots. In the absence of any other source of hemorrhage the conclusion was unavoidable that these small veins, engorged from the pressure of the adjacent myoma, and especially so just before the menstrual epoch, had ruptured and had been bleeding more or less continuously since the first fainting attacks three nights before. Only thus could the enormous amount of blood found in the abdomen be explained in view of the very small venous tears. The fact that no hemorrhage was taking place at the time of operation could easily be explained by the exsanguinated condition of the patient. The operation consisted in removal of the fibroid tumor and ligation of the veins. The patient stood it fairly well; the next day the menses appeared, and normal recovery took place. Two and a half months later the patient was in good health save for a certain degree of anemia.

DISEASES OF THE LARYNX AND CONTIGUOUS STRUCTURES

UNDER THE CHARGE OF

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Death of a Child during Suspension Laryngoscopy.—TURNER (*Jour. Laryngol.*, August, 1916) reports this case: A female infant, aged two and a half years, had undergone frequent reintubation for diphtheria during a period of nine weeks. One month after dismission from hospital severe dispnea recurred and she was submitted to examination by suspension laryngoscopy under anesthesia after preliminary injection of $\frac{1}{200}$ grain of atropin. Respiration ceased immediately upon introduction of the tongue spatula. This was removed at once and artificial respiration instituted but without obtaining the desired effect. Tracheotomy was rapidly performed and artificial respiration again resorted to, but without success. The right vocal cord had a somewhat uneven outline, and the mucous membrane beneath it was edematous.

Diffuse Diabetic Ulceration of the Pharynx and Larynx.—ARROWSMITH (*Laryngoscope*, September, 1916) reports a case, the seventh on record it is intimated, in a woman, aged sixty-six years, who, for about a year, had suffered from gradually increasing dysphagia, and at times regurgitated liquids through the nose on attempts at swallowing them. Wassermann tests and sputum examinations negatived syphilis and tuberculosis. Recalling a similar case observed about 1890 in the practice of his friend Dr. Westerbrook, a somewhat similar instance in

his own practice, and a report by Dr. Friedenthal of 5 cases of diabetic ulceration of the pharynx and larynx, he decided that this case belonged in that category. A twenty-four-hour specimen of urine yielded between 4 and 5 per cent. of sugar. The institution of the Allen scheme of treatment produced decided improvement of the glycosuria, but without much change in the local condition. There was ulceration of the uvula, the retina, the posterior wall of the pharynx, and of the laryngeal surface of the epiglottis, and the right arytenoid.

An Epi-hyal Bone in a Human Subject.—GUTHRIE (*Jour. Laryngol.*, July, 1916) reported this case to the Laryngological Section of the Royal Society of Medicine. It occurred in a man about fifty years of age suffering from carcinoma of the upper end of the esophagus. A radiogram by Dr. Oram showed a chain of bones apparently representing a complete "hyoid arch," composed of the basi-hyol (body of hyoid), cerato-hyal (short process of hyoid), epi-hyal, and stylo-hyal, the condition being similar to that seen in the dog.

The Upper Respiratory Passages in Habitual Users of Cocain and Heroin.—RIDPATH (*Laryngoscope*, January, 1916) has carefully examined a number of instances of sniffers of these drugs and finds that the constant use of heroin or cocain upon a mucous membrane produces congestion and tumefaction followed by atrophy and anemia; but the sensibility of the mucous membranes is not affected. Catarrhal affections are less prevalent than in non-users of the drugs. Heroin produces a thin acrid discharge, and cocain causes epistaxis.

Vernal Catarrh Cured with Radium.—DELAVAN (*Radium*, November, 1916), in an article on Radium in the field of Laryngology states that the Radium Institute of London reported excellent results in the treatment of "Vernal Catarrh," patients treated for it with radium having in a large proportion of cases been cured without recurrence, although under observation for a series of years.

Tuberculosis of the Frontal Sinus.—THOMAS (*Jour. Am. Med. Assn.*, July 24, 1915) reports two cases, and states that but five in all have been reported previously and of which he gives a synopsis. Of these five, four terminated fatally, and the other had remained well seven months after operation. Of the author's cases one recovered after two operations and had remained well for more than two years. The other case had been subjected to an extensive intranasal operation two years before consulting Dr. Thomas. It is reported as a case of tuberculous frontal sinusitis, with osteomyelitis, epidural, subdural, and cerebral abscesses resulting in death; a necropsy having been held.

Bleeding Polypus of the Turbinate Body.—MATSUI (*Laryngoscope*, February, 1916), in an article on the "Turbinal Origin of Bleeding Polypus of the Nose," states that he had seen two cases in the clinic of Prof. Ino Kubo, both of which grew out of the lower turbinal and

bled constantly. They are reported in detail and their minute anatomy described and depicted. The tumor parenchyma of these growths is made up of an increase in connective tissue and vessels, and according to the preponderance of one or the other element they may be termed fibroma, angioma or fibro-angioma. They originate from the tissue of the gland stratum of the nose.

Papilloma of the Nose.—CALLISON (*Laryngoscope*, March, 1916) reports the detailed study of a true papilloma or papillary fibroid springing from the region of the middle turbinate, bulla and infundibulum, in a colored female forty years of age.

Safety-pin Expelled from the Esophagus into the Rhinopharynx During Anesthesia.—KAUFMAN (*Laryngoscope*, September, 1916) reports the case of a female, aged nineteen years, who swallowed an open safety-pin which was located by roentgen ray at about four and a half inches down the esophagus. Ether was administered and caused much retching and vomiting. Thorough exploration of the esophagus revealed only a few punctate hemorrhages but no pin, It was assumed that the pin had passed into the stomach, but roentgen-ray inspection of the stomach did not reveal the pin. Dr. Bird then roentgen-rayed the head, and detected the pin lodged in the postnasal space, when he removed it with little difficulty.

Treatment of Traumatic Salivary Fistula of the Parotid by Immobilization.—PIETRI (*Rev. de laryngol., d'otol. et de rhinol.*, March 15, 1916) describes a number of cases of salivary fistula following gunshot wounds, and details the various treatments instituted. None of them, it is said, can compare with the efficiency of simple absolute repose of the jaws, and feeding the patient with liquids through a tube, the treatment requiring several weeks of patience. Some twenty to thirty cases were observed and cured, and some of the most characteristic of them are pictured in the context.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Dietary Deficiency as the Etiological Factor in Pellagra.—VEDDER (*Arch. Int. Med.*, August 1, 1916, xxviii, No. 2) presents the conception of deficiency diseases which has been formed during the study

of beriberi and scurvy. This conception is that there are certain hitherto unknown chemical substances called vitamins which are present in small, varying amounts in foodstuffs. A definite supply of these substances is necessary to maintain normal metabolism, and if a group of people live on a diet deficient in any one of these vitamins the corresponding deficiency disease is produced in a certain number of these people. In the case of beriberi, people living exclusively on over-milled rice, which is deficient in the beriberi preventing vitamins, develop the disease. If a group of people live for a period on food deficient in scurvy vitamins, a number of them will develop scurvy. A deficiency disease is very different from malnutrition, for the scurvy patients' diet may contain an adequate amount of proteins, fats, carbohydrates and inorganic salts and yet may lack certain definite chemical substances, the vitamins, which prevent scurvy. Each individual requires a definite quantity of these vitamins to maintain normal metabolism and this amount varies with the individual. Taking into consideration these facts in respect to known deficiency diseases, scurvy and beriberi, the author puts the query, "Is it possible to consider pellagra as a deficiency disease?" He considers the evidence on this point under the following heads: (1) What analogies exist between pellagra and the two proved deficiency diseases, beriberi and scurvy? (2) Can the evidence pointing toward infection be reasonably explained according to a deficiency hypothesis? (3) Is any deficiency demonstrated in the diet of pellagrins? (4) Can the great increase in pellagra during recent years be explained by the deficiency hypothesis? (1) Pellagra shows great similarity to beriberi and scurvy with regard to clinical and pathological phenomena. The condition of the gums and mouth, the gastro-intestinal lesions, the nervous symptoms in pellagra and scurvy show marked similarity. There are also similarities existing between pellagra and beriberi. The condition of the intestine is somewhat alike in these two diseases, and considerable likeness in the lesions of the nervous system and in the symptomatology referable to the nervous system has been noted. Analogies exist between the epidemiologic data in pellagra and beriberi, both being closely associated with poverty and poor diet. Both these diseases are extraordinarily frequent in institutions, especially hospitals for the insane. The history of the investigations as to the cause of these two diseases is alike in many respects. Although all these analogies prove nothing definite yet they are very suggestive in considering the question of whether pellagra is a deficiency disease. (2) The evidence pointing toward pellagra as an infection may be explained if the hypothesis that pellagra is due to a dietery deficiency be assumed. It may seem impossible that the very pronounced lesions caused by the disease are due to a mere dietery deficiency but the pathologic condition observed in other deficiency diseases, namely, scurvy and beriberi is just as severe. Another piece of evidence pointing to pellagra as an infectious disease is the tendency to self-limitation of the attacks in the absence of specific therapy and presumably without any change in the defective diet that produced the disease. Since it has not been determined which foods contain the necessary vitamins to prevent pellagra it might be possible for the patient to receive some nourishment which has supplied the deficiency and therefore caused improvement. The converse of

this proposition has also been stated that pellagra patients sometimes become worse and die in spite of the fact that they are having apparently an excellent diet. But this diet may have been deficient in the necessary vitamins or the patient may have been unable to assimilate them. Furthermore, it is an authenticated fact that patients with dry beriberi often die although they are fed on the proper diet because the disease has progressed to such a point that death is imminent. The fact that pellagra appears in the spring and improves during the summer and fall to recur again the next spring points distinctly toward the dietary hypothesis and not toward the infection theory as no known infection acts in this way while beriberi acts exactly in this way. This action of the disease is thought to be due to the dietary habits of the people, that is, the poor live chiefly on flour, cornmeal, canned goods and salt meat in the winter and such diet after several months produces the lesions which appear in the spring. When fresh vegetables and fruits appear in the late spring and early summer, the deficiency is remedied and the condition improved. Although the statement that in about 90 per cent. of the cases studied there was personal contact or association with a previous case of pellagra seems to be strongly in favor of the infectious nature of the disease, it is really of little significance, for 43.5 per cent. of these contact cases have occurred among members of the same family who have presumably the same diet. As to the remaining 46.5 per cent., where contact with a case outside the family has been demonstrated, it may be said that pellagra is so common in many parts of the south that really every one has come into contact or associated with a case of pellagra. The fact that a very large part of the population has been in contact with cases without developing the disease takes away from the importance of contact as an etiologic factor as does the fact that doctors, nurses and attendants in closest contact seldom acquire the disease. Density of population seems to bear no relation to the spread of pellagra, as in Spartanburg, S. C., the mill villages present a rate of 142 cases per 10,000, while the rest of the city population living under the same conditions of congestion gives only 29 cases per 10,000 inhabitants. The greater number of cases in the mill villages is explainable if it is granted that pellagra is a deficiency disease, as the population of these villages is a homogeneous group of people of the same economic status living on a poor class of food. The Pellagra Commission collected considerable evidence to show that proximity of domicile was an important factor in the incidence of pellagra and that, since this was true, the disease must be of infectious origin. They found that new cases of the disease developed almost exclusively in small foci within which one or more cases of the disease already existed, the greatest number occurring in the first zone, the next in the second and the least in the third. However, it seems that this incidence of cases can be explained if the disease is caused by a dietary deficiency as the majority of people living in the house with a pellagra patient, that is, those included in Zone 1, would be exposed to the same deficiency of diet. The large number of the cases in Zone 2 is explained by the fact that pellagra is commoner among the poor than among the well-to-do and the poor people live in the same part of a town or village and so are practically segregated. Therefore there would naturally be more cases in the neighborhood immediately

surrounding the house where a case existed than there would be in a remote and more prosperous section of the city. While there is a tendency for pellagra to occur in that part of a community having primitive systems of disposal rather than in the part having proper sewage systems, this proves nothing, for the poorer sections which have the less developed systems, are the sections where poverty and, consequently, a poorer dietary exist. The commission has shown a tendency to believe that, because they have not found any special food to be the causation factor, the disease could not be of dietary origin, and that if it were a deficiency disease, fresh meat, milk and eggs might be supposed to supply this deficiency. They have collected evidence to show that of the 82 persons in families using fresh meat daily, 4.88 per cent were pellagrins. This evidence is not considered conclusive because (1) it does not consider in sufficient detail the quantities of the various foods used; (2) it considers individual foodstuffs and their influence rather than the total diet; (3) the possibility that wheat-flour is mainly responsible for the deficiency has not been investigated sufficiently; (4) in an investigation of the diet of pellagrins it was found that among both the poorer and the well-to-do cases, there were some circumstances as a result of which the patient had lived on a very one-sided diet, in every case consisting chiefly of flour, corn products, or potatoes, with the addition of salt meat or canned vegetables; (5) pellagra is becoming more common in the south every year and an attempt has been made to explain this in accordance with the hypothesis that it is due to a dietary deficiency. The following facts indicate that changes have occurred in the dietary of the population as a whole during the last ten years: (1) The population itself has increased greatly, especially the industrial population among which the dietary is distinctly inferior to that of the remainder of the population. (2) There has been a great change in the purchasing power of the population, but there has also been a greater increase in the price of food so that there is a distinct tendency for poorer people to cut down the consumption of fresh meat, eggs, vegetables, and fruit and to increase the consumption of such staples as cornmeal, hominy, and flour. (3) Such tendencies were actually demonstrated in a number of cases investigated and statistics were collected which showed that the per capita consumption of fresh meat and of pure lard had decreased very considerably in the last ten years while the consumption of canned goods, cornmeal, and flour had increased. As a result of the investigations the conclusion is reached that the hypothesis that pellagra is caused by a dietary deficiency seems very plausible, and must be considered in subsequent studies of the disease.

How Tuberculosis is Contracted.—SMITH (*Jour. Med. Research*, 1915, xxxii, 417) states that the beginning of the tuberculous changes in the wall of the minute bronchi is not in itself proof that the bacilli are air-borne, nor does it prove that inhaled bacilli have penetrated directly the mucosa of the minute bronchia. The development of tuberculosis in the apical lobes in man is best accounted for by the less active aëration and less active lymph current. Rib pressure may contribute toward fixing the bacilli. Bacilli, deposited either from the

air or the blood in other lobes are either destroyed or promptly carried by the lymph current to the lymph nodes, where they are gradually destroyed. The phenomenon of phthisis in man is strong evidence that the human being possesses a relatively high degree of resistance to the tubercle bacillus.

Arsenic in "Chemically Pure" Zinc.—MYERS (*Public Health Reports*, October 6, 1916, vol. xxxi, No. 40) examined eight samples of metallic zinc purporting to be chemically pure and free from arsenic and found them to contain arsenic. After specifications were submitted requiring arsenic-free zinc, samples of impure zinc were also received. Amounts varying from 1 to 10 parts per 1,000,000 of metallic arsenic were found. This fact shows that it is necessary for analysts in food, drug, and public health laboratories to examine all chemicals for themselves.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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The Specificity of Streptococci.—Much has appeared in recent literature indicating the importance of streptococci in human disease. Various authors have approached the subject from different angles. Some have been content with isolating these microörganisms from tissues and offering this evidence as demonstrating the causative factor in the disease, others have studied the streptococci from various sources hoping to find a means of classification which would indicate their biological and pathogenic qualities, a third group has attempted to distinguish the streptococci only by their ability to locate in particular regions and induce disease in them. HENRICI (*Jour. Infect. Dis.*, 1916, xix, 572) studied 53 strains of streptococci from various sources, comparing the cultural characters with the pathogenic qualities as exhibited in infection of rabbits. The streptococci used were classified according to the method of Andrewes and Horder using the hemolytic test to divide the two main groups. Two hundred and twenty-five rabbits were inoculated with varying amounts of culture and were autopsied at intervals of two to ten days. Careful observations were recorded and tissues were studied microscopically. The author found lesions in the brain, heart, arteries, muscles, joints, and kidneys. In no

instance were the lesions in any one of these tissues produced by a single type of streptococci alone. It was quite remarkable that inflammatory processes induced by the streptococcus pyogenes were not uncommonly identical with those produced by the viridans group. In only a few instances were abscesses found. From these results it would appear that the strains of hemolytic streptococci used in the experiments were of low virulence. The author could find no evidence that any of the organisms tested showed an elective affinity for particular tissues. Valvular heart lesions developed in about 9 per cent. of the rabbits inoculated with non-hemolytic strains and in 11 per cent. of those receiving hemolytic streptococci. Myocardial lesions simulating those found in acute rheumatic fever occurred with equal frequency in animals receiving the hemolytic or the non-hemolytic varieties. He concluded that from the evidence obtained from the experiments we are not justified in recognizing any particular class of streptococci as specific for rheumatic fever. In general he found the hemolytic streptococci more virulent than the non-hemolytic, although the two classes localize in the same tissues with equal frequency.

Multiple Telangiectatic Hemangiomata.—Cutaneous hemangiomata are quite common and are quite frequently seen about the face. Many of them appear to have a congenital origin although they may not be observed until, by increase in size, they form a definite tumor mass in early years of life. It is not uncommon to find these vascular tumors progressively enlarging and sometimes even recurring after removal. The question of malignancy has given rise to much discussion although metastatic growths have not been demonstrated. This type of tumor is not common in the internal organs. SCHMITT (*Cent. f. Path.*, 1916, xxvii, 145) describes a case of hemangioma arising in a child of three months and making its simultaneous appearance in two situations. The one was lying in the orbital fossa and was recognized clinically and removed by operation. At autopsy, a few days later a second mass was found along the trachea in close proximity to the right thyroid. The histological character of the tumor simulated an angioma simplex with evidence of progressive extension of the capillary structure into the surrounding tissues. This infiltrating character of the growth has led numerous authors to classify these tumors among the sarcomata. The capillary structures forming the main element in the tumor are seen as wormy masses with thick walls composed of endothelial overgrowth. At times the lumina are well preserved or even dilated, and at others, the lumen is occluded by the proliferated tissue so that no blood elements are to be found within them. A number of other cases of multiple angiomata have been described by other authors. In some of them skin tumors were associated with similar structures in the internal organs. The wide distribution of the tumors in some of these cases is quite remarkable, but yet there is no evidence of true metastatic implantation. It would rather appear that we are dealing with multiple primaries.

Histological Lesions in Pellagra, Fasting and Experimental Scurvy.—Not a few of the studies carried out upon nutritional diseases and particularly pellagra have been made by the Italians. In fact, much

of the earlier work indicating the relation of corn to pellagra began with the studies of Ballardini. For the group of manifestations arising from the eating of deteriorated corn they have coined the term "maidism." According to its use the word may be applied to various clinical and pathological manifestations making their appearance at various stages during the nutritional disturbances. RONDONI and MONTAGNANI (*Sperimentale*, 1915, lxix, 659) have again reviewed the pathological changes occurring not only in "maidism" but also in scurvy and fasting. They point out that a comparison of the histological lesions is essential for a proper understanding of each. The fasting experiments were made upon guinea-pigs, observations being made upon both the acute and chronic types. The outstanding features were general emaciation, atrophy of organs, especially spleen and liver; enlargement of adrenals. In another series of experiments, guinea-pigs were fed on corn flour and histological studies were made upon the animals dying spontaneously. In these animals petechial hemorrhages were occasionally seen in various organs. The liver showed evidence of degeneration as well as proliferation of the bile ducts and liver cells. Central hyperemia was also common. The heart, lungs, intestine, kidney and pancreas showed no evidence of change other than occasional hemorrhages. The spleen showed evidence of fibrosis about the central arteries and the organ was slightly increased in weight though not in size. The authors claim to have observed fairly constant changes in the thyroid, consisting of a hyperemia, hyperplasia and increase in the colloid content. Occasionally patches of fibrosis also appeared within the thyroid. A similar hyperemia and hyperplasia was found in the adrenals, being particularly marked in the cortex. The medulla showed but little change. The important changes observed in the central nervous system were in the cord in which the ganglion cells of the anterior horn showed evidence of degeneration. Less marked degeneration was present in the cerebellum. They conclude that exclusive corn feeding may produce lesions more or less serious in many organs and tissues, which explains the cachexia and death of the animals. Of particular interest were the lesions of the thyroid and suprarenal in which a degree of sclerosis may be associated with the functional disturbances. The sclerosis of the thyroid differentiates the "maidism" from simple emaciation. "Maidism" can be differentiated from scurvy by the presence of the sclerosis in the former and the predominant hemorrhages in the latter. Furthermore the degenerations in the nervous system are more marked in "maidism." The authors suggest that "maidism" may be the result of toxic substances present in good corn or the deficiency in corn of a certain unknown product necessary for the normal development and function of the glands of internal secretion.

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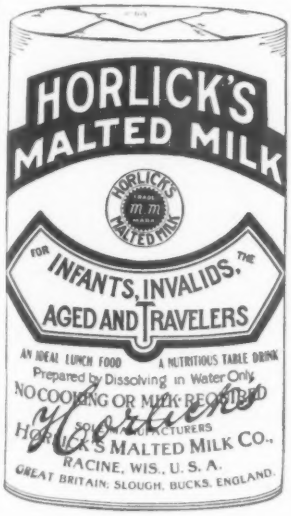
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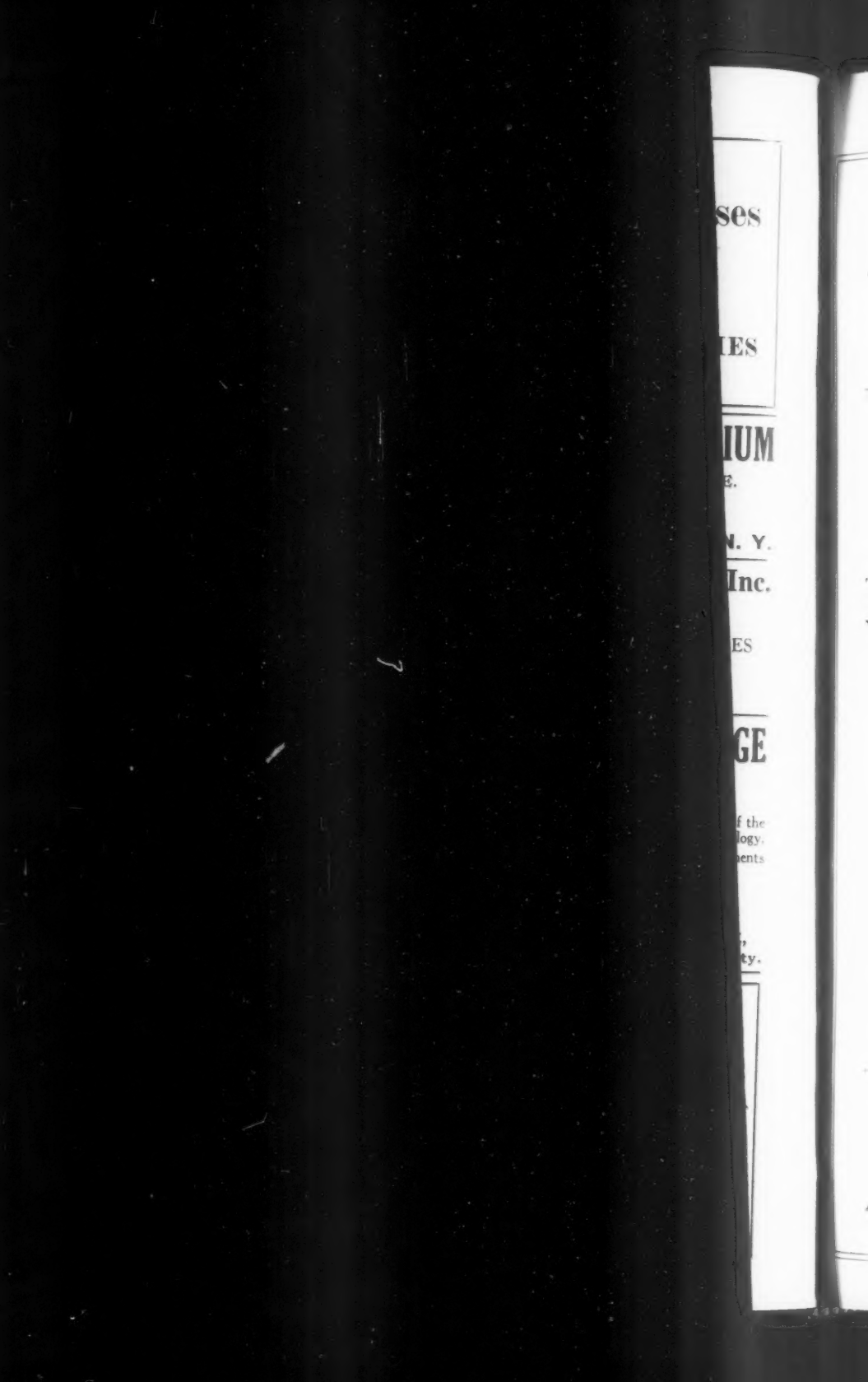

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